Self-Regulation, Physical Activity and Unexplained Chronic Fatigue

From determinants to Interventions

Marta M. Marques

Marques, M.M.
Self-regulation, Physical Activity
and Unexplained Chronic Fatigue:
From determinants to Interventions
Dissertation Leiden University

ISBN: 978-989-20-5082-9

This research was supported by a grant of the Portuguese
Science Foundation (SFRH/BD/47579/2008).

Layout and cover design
Mariana Marques

Printed by Greca – Artes Gráficas, Lda, Portugal

Self-Regulation, Physical Activity and Unexplained Chronic Fatigue

From determinants to Interventions

Proefschrift
ter verkrijging van de graad van
Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus
prof mr. C.J.J.M. Stolker, volgens
besluit van het College voor
Promoties te verdedigen op
Dinsdag 13 Januari 2015 klokke
15:00 uur

door
Marta Moreira Marques geboren te
Porto (Portugal) in 1981

Promotiecommissie

Promotor
Prof. Dr. C.M.J.G. Maes

Co-promotor
Dr. V. M. J. de Gucht

Overige leden
Prof. Dr. Ph. Spinhoven
Prof. Dr. G. Crombez, Universiteit Ghent, België
Prof. Dr. P. J. Teixeira, University of Lisbon, Portugal
Dr. M.W.M. de Waal, Leids Universitair Medisch Centrum

Table of Contents

01

General Introduction

Fatigue is a common symptom in adults worldwide, varying in length (acute to chronic) and severity [1]. Occurrence of fatigue can be medically explained (e.g. related to chronic disease), but in some cases fatigue (physical and mental) symptoms are medically unexplained, i.e. cannot be adequately explained by organic causes. Unexplained fatigue is considered to be chronic (chronic fatigue - CF) if it lasts for at least 6 months.

Persistent and severe unexplained fatigue is not alleviated by rest, is debilitating, and leads to functional and social impairment (e.g. inability to work). Commonly, these patients experience additional rheumatologic and neuropsychiatric symptoms, namely pain and cognitive impairment [2, 3]. When at least four of these symptoms are present it is diagnosed as Chronic Fatigue Syndrome (CFS), according to the US Centres for Disease Control and Prevention (CDC) criteria [4], which is the most widespread criteria in research and clinical practice. Another case-definition commonly used is based upon the Oxford Criteria [5], a less restricted set of criteria not requiring the presence of additional somatic symptoms. Table 1 presents the characteristics of these case definitions.

A panel of experts has recently proposed a new international consensus case definition [6], which does not establish a timeframe for the presence of fatigue, but requires the presence of postexertional malaise (i.e. increase in fatigue following intense effort) as well as additional clusters of symptoms related to neurological, immune, gastro-intestinal, genitourinary, and energy production/transportation impairments. One of the problems with diagnosing CF or CFS is that the primary symptom, fatigue, is difficult to define and to measure due to its subjective nature; there is no biological marker for CF(S) [7, 8]. The diagnosis of CF or CFS is thus exclusionary [9]. In terms of terminology, another name also used for CFS is Myalgic Encephalomyelitis/ Encephalopathy (ME). Some researchers consider this term to be more appropriate to characterize the complex nature of the disease [8].

CFS is considered to be a heterogeneous clinical condition. Patients may present with different levels of (mental and physical)

fatigue, psychological distress, additional somatic symptoms, impairment and disability [3, 10]. Co-morbidity between CFS and psychological distress (depression and anxiety) was found in several studies, although the relationship remains unclear [3, 11]. Patients with CFS also experience a great number of other somatic complaints [8, 12]. In addition, studies report a percentage between 35% to 70% of CFS patients that present with both CFS and Fibromyalgia [8, 13].

Table 1 Criteria of the main CFS case definitions

CFS criteria	**Oxford**	**CDC (1994)**
Inclusion criteria	Fatigue is the principal symptom. Definite onset that is not lifelong. Fatigue is severe, disabling, affects physical and mental functioning. Fatigue should have been present for a minimum of 6 months during which it was present for more than 50% of the time. Other symptoms may be present, particularly myalgia, mood and sleep disturbance.	Medically unexplained, persistent fatigue lasting for at least 6 months, of new onset, not due to ongoing exertion or organic disease, not substantially relieved by rest, and leading to a significant reduction in activity levels.[1] Presence of four or more of the following symptoms: • lengthy malaise after exertion impaired memory or concentration • unrefreshing sleep • joint pain without swelling or redness • muscle pain • headaches of a new type or severity tender cervical or axillary • lymph nodes • sore throat
Exclusion criteria	Medical conditions known to produce chronic fatigue. Patients with a current diagnosis of schizophrenia, manic depressive illness, substance abuse, eating disorder, proven organic brain disease.	Medical conditions known to produce chronic fatigue. Patients with a current diagnosis of Major depressive or bipolar disorder, psychotic disorder, dementia, eating disorders, alcohol and substance abuse, and severe obesity.

[1]*If symptoms do not fulfil the criteria for CFS, the condition is referred to as idiopathic chronic fatigue* (ICF)

Chronic fatigue is reported by about 6% of the general population [14]. Prevalence of CFS has been reported to be in between 0.007% and 2.6% in community and primary care samples. Prevalence rates vary according to several factors such as the setting, country and diagnostic criteria used [14]. Most studies on the prevalence and clinical characteristics of CF and CFS have been conducted in North-Western Europe, North America and Oceania [15], and there are very few international studies that compare patient populations from different countries [16, 17]. It is more prevalent in younger adults (less than 40 years of age) and among women [2, 3, 8]. In terms of prognosis, full recovery rates are low; it is more common for patients to experience improvements in symptom severity [18]. Chronic fatigue is associated with a high use of health care resources and represents an important socioeconomic burden [2, 19].

Aetiology of Chronic Fatigue

The aetiology of CF(S) remains unclear. Still, research points towards a multifactorial nature that consists of a combination of biological/physical and psychosocial factors (biopsychosocial model) operating as predisposing, precipitating and perpetuating factors of chronic fatigue [3, 8, 9, 20].

Predisposing factors are those that make the person more vulnerable to develop chronic fatigue, such as genetics, personality factors, prior psychiatric disorder, and overactive lifestyles, among others [3, 8, 9]. Precipitating factors are those that trigger fatigue, such as acute or chronic physical (e.g. viral infection, surgery) and psychological stress (e.g. serious life events) [3]. Perpetuating factors contribute to the chronicity of fatigue, and can impede recovery from CF(S) [21]. Research has identified several perpetuating factors, such as biological changes (e.g., changes in the hypothalamic-pituitary-adrenal axis), presence of additional somatic symptoms (e.g. pain), social factors (e.g. lack of social support), psychological distress (depression and anxiety), as well as cognitive and behavioral factors, which

are considered to play a major role in the maintenance of fatigue [9, 20, 21]. Regarding cognitive factors, negative or maladaptive illness perceptions (e.g. poor sense of control over symptoms or somatic attributions of symptoms), and coping strategies (e.g. catastrophizing, passive coping) have been identified as perpetuating factors of fatigue [20, 22].

Prolonged physical inactivity (rest) and decreased physiological exercise capacity are considered major perpetuating behavioral factors of symptoms in CF(S) [23, 24]. It has been suggested that prolonged inactivity can result in physical deconditioning as well as in other physiological and psychosocial consequences that may perpetuate fatigue severity and physical disability [23, 25, 26]. On the other hand, high levels of physical activity that exceed personal physical capacity can cause overexertion and perpetuate fatigue symptoms [23, 27-29]. It is therefore common to find a "all-or-nothing" (or " boom-and-bust") behavior pattern in these patients, which is the systematic alternation between periods of over-activity (when feeling good) and, as a consequence of that, feeling extremely fatigued and having to rest for longer periods of time [9, 23, 30]. Some patients continue to perform their daily activities even when symptoms get worse (overactive pattern), but most patients present reduced levels of daily activity [23, 31]. Patients' perceptions and expectations with respect to symptom exacerbation as a consequence of physical exertion (postexertional malaise) can also lead to an avoidance and fear of physical activity [3, 26, 27] that does not correspond to the actual level of physical disability.

Available research shows that patients with CFS have at average lower levels of physical activity, less muscle strength and a worse physiological exercise capacity [24, 25, 31], than healthy sedentary control subjects. It has therefore been recommended that patients with chronic fatigue engage in (balanced) physical activity instead of refraining from it.

Research is still limited with respect to the most appropriate type of physical activity for chronic fatigue management but recent literature points at the beneficial effect of aerobic activities (e.g. walking), performed at mild and moderate levels of intensity [23].

Current behavioral and psychological treatments

Treatment approaches for CF(S) focus on perpetuating factors, especially on behavioral (physical activity) and psychological factors, in view of reducing severity of fatigue and other symptoms as well as improving functioning and quality of life. Graded Exercise Therapy (GET) and Cognitive Behavioral Therapy (CBT) are the current recommended non-pharmacological treatments for chronic fatigue management [3, 8, 32]. Based on a physiological model of deconditioning, GET is an aerobic exercise therapy, consisting of supervised exercise sessions and/or home-based exercise prescription (e.g. walking). In GET, physical activity is initiated at a level that (a) takes into consideration patients' initial level of exercise capacity and (b) doesn't exacerbate symptoms. Exercise is then gradually increased in frequency and intensity until patients reach an optimal level of activity. GET focuses on avoiding overexertion by advising patients not to exceed the recommended levels of physical activity/exercise. At the same time, patients are encouraged not to reduce or stop doing physical activity when symptoms get worse. Graded exercise programs follow the exercise prescription guidelines from the American College of Sports Medicine [33], tailored to each patient's level of physical capacity [34]. GET has shown to have moderate beneficial effects upon chronic fatigue management [35-37].

CBT and other psychological approaches consider not only behavioural factors, but also cognitive and affective factors that may contribute to the maintenance of fatigue symptoms. The primary focus of CBT for these patients is on challenging cognitions related to the perpetuation of symptoms and distress (e.g. somatic illness attributions, perceived lack of personal control, focusing on physical sensations) as well as on planning work and functional recovery [38, 39]. Because of the empirically established benefits of physical activity in CFS, a large number of Cognitive Behavioural Therapy (CBT) trials have incorporated a graded physical activity/exercise component. Focusing on a cognitive model of avoidance of physical activity, patients are encouraged to engage in a gradual

increase of physical activities and balance daily activities [3]. Some CBT approaches distinguish between relatively-active (characterized by an alternation of over-activity and rest) and low-active patients [3, 39]. In the first case patients are initially encouraged to balance their daily activities and rest, but for both groups of patients the intervention focuses on a gradual increase of physical activity levels. Cognitive-behavioral therapy (CBT) has also demonstrated to have beneficial effects on chronic fatigue management [36, 37, 40].

Some recent GET, CBT and combined approaches (e.g. multidisciplinary rehabilitation treatments) [41] also use pacing strategies, either by allowing flexibility in graded exercise goals or programs (e.g. duration of session) according to individual tolerance levels (e.g. stop if symptoms get worse) [27, 42] or by promoting a balance between physical daily activities and rest according to patients own symptoms and capability [27, 41].

Two meta-analyses comparing GET and CBT have not found differential effects between both treatments on fatigue management [36, 37]. Despite the fact that physical activity seems to be an important component of both treatment approaches, there is little research on the effects of GET and CBT on physical activity, with some studies showing only marginal or trivial effects [43, 44]. One of the problems with both GET and CBT is that both interventions are resource-intensive [36, 37]. Recent randomised controlled trials have tried to overcome this limitation by conducting minimal contact interventions based on self-guided instruction manuals and remote contact showing promising results [45-47]. These brief interventions have the advantage that they can be more easily implemented in standard health care, e.g. in a primary care setting. Other non-pharmacological treatments such as complementary and alternative therapies, as well as pharmacological immunological treatments have been developed but results from these trials are inconclusive [48].

Promoting (balanced) physical activity: The Role of Self-Regulation

Adopting a health behavior change framework can contribute to the understanding and long-last promotion of physical activity in chronic fatigue patients. One of the most prominent perspectives on health behavior change is Self-Regulation (SR) theory [49-52]. According to this theory, behavior is a goal driven process [50]. SR can thus be defined as a "sequence of actions and/or steering processes intended to attain a personal goal"[49]. This dynamic-goal guided process occurs in phases, consisting of a goal selection and goal setting phase, an active goal pursuit or action phase, and a goal attainment and maintenance or disengagement phase, in which motivational and volitional aspects interact [49]
A central aspect in SR is that individuals set personal important and meaningful goals [49, 52]. Research points out that formulating self-chosen and personally important goals to guide behavior (goal ownership), as well as autonomously regulate one's own behavior, increases the likelihood of goal achievement and maintenance [49, 53]. Goals are hierarchically structured and interconnected, with more abstract long-term goals (e.g. be healthy), generating input for the formulation of short-term concrete goals such as specific actions (e.g. exercise three times a week) [52]. This hierarchical goal structure is important for health behaviour change interventions as it considers that specific actions or concrete goals such as doing physical activity will only be formulated and pursued by individuals if they are linked to higher hierarchical goals such as being healthy. At the same time it stresses the importance of increasing the personal relevance of health goals in order to increase the likelihood of adopting physical activity goals. One of the triggers of motivation and intention to change behavior is the perceived discrepancy between an individual's current state (input value) and a desired state (the reference value), leading to the formulation of a specific goal [52]. The significance of these SR processes for interventions in chronic fatigue is that they cannot only contribute to our understanding of the influence of life goals on chronic fatigue patients' behavior and treatment adherence [54], but interventions based upon these models may also contribute to

change the reference value from symptom avoidance to well-being and encourage patients to change their personal goals to more active and positive goals [54, 55].

Additional SR cognitions and skills are considered to play an important role in the phases of the goal guiding process, and thus in promoting long-lasting health behaviour change [49]. Goal self-efficacy, formulation of self-chosen and personally important goals (goal ownership), planning, control over competing goals, self-monitoring, feedback and anticipatory coping, as well as attention and emotion control, are considered to add great value to the transition from a motivational phase (goal selection) to action phases of goal pursuit. Relapse prevention strategies such as coping planning, as well as satisfaction and ownership of the changed behaviour or goal reformulation are additional SR factors that can contribute to long-lasting health behaviour change [49].

Self-regulation based interventions have demonstrated to be effective in promoting long-lasting health behaviour change in chronic disease populations [56-59]. In a recent meta-analysis, Michie et al. [60] found that interventions combining self-monitoring with other skills derived from Self-regulation theory (i.e. Control Theory [52]), such as goal setting, provision of feedback, planning and goal revisiting, were more effective in promoting changes in PA and healthy eating in the general population than other intervention not using these techniques. The moderation effect of SR-skills in interventions effect were also found in other meta-analysis of trials conducted with chronic diseases patients [61-63]. For that reason, a self-regulation perspective was adopted to develop an intervention for CF(S) patients.

Aims of the thesis

Several behavioral and psychological treatments have been developed for chronic fatigue patients, focusing on physical activity, which is considered a key factor in chronic fatigue management. Research is however limited with respect to the effects of these interventions on physical activity. Furthermore, many of these interventions focus on establishing/prescribing structured exercise plans and less on the role of motivational and self-regulatory factors in the successful adoption and regulation of physical activity and other behaviours that can lead to a reduction of fatigue severity and improvement of patients' functioning and quality of life.

The objectives of this thesis are to:
1. Adapt the Checklist of Individual Strength (CIS20), a valid and reliable measure of fatigue severity, for a Portuguese population in order to measure fatigue according to international standards.

2. Investigate the differences in clinical characteristics and behavioral and cognitive determinants on chronic fatigue in a Dutch and a Portuguese patient sample.

3. Examine the effects of behavioral and psychological treatments containing a graded exercise component in chronic fatigue management as well as to examine potential moderator effects of trial characteristics.

4. Develop and evaluate post treatment and medium-term effects of a self-regulation based intervention (4-STEPS), combining motivational interviewing and self-regulation skills training, on physical activity and chronic fatigue management.

5. Analyze whether changes in physical activity and use of self-regulation skills explain observed effects of the 4-STEPS intervention on fatigue severity.

Outline of the thesis

This thesis consists of eight chapters. This first chapter (**Chapter 1**) provided a general introduction on chronic fatigue, its management and the contribution of a self-regulation perspective to available behavioural and psychological treatments targeting physical activity. The following six chapters (Chapters 2 to 7) correspond to empirical studies either published or submitted to peer-review journals in the field of psychology and health.

The first of these studies (**Chapter 2**) describes the psychometric properties of the Portuguese version of the Checklist of Individual Strength (CIS20-P;[64]). The CIS20 is a well-validated multidimensional measure assessing fatigue severity that has been used in several observational and intervention studies conducted in chronic fatigue patients [45, 65]. Fatigue severity is the primary endpoint in many interventions conducted in chronic fatigue patients, including the trial presented in this thesis. Hence, in research studies conducted in Portuguese speaking populations it is crucial to use a Portuguese validated measure to assess fatigue severity.

Chapter 3 explores cross-cultural similarities and differences in clinical characteristics and behavioral and psychological determinants of CFS between a Portuguese and a Dutch CFS patient sample. Due to the fact that there is no published research conducted with CFS patients in Portugal, and that most trials targeting these patients are done in Northern European countries, this comparison is important in view of developing culture relevant behavioral and psychological treatments for CFS.

Chapter 4 presents an updated systematic review and meta-analysis of the effects of behavioral and psychological interventions with a graded physical activity component on fatigue severity, physical functioning, physical activity, and psychological distress, among patients with ICF/CFS. Potential moderator effects of trial characteristics were examined in order to identify factors of success that can improve interventions' design and effectiveness.

Chapters 5, 6 and 7 describe the development, implementation and evaluation of a randomized controlled trial (RCT) for

patients suffering from chronic fatigue, the "Four steps to control your fatigue (4-STEPS)" trial. This RCT, conducted in Portugal, compared a brief self-regulation based physical activity program consisting of motivational interviewing and self-regulatory skills training (4-STEPS) to a control condition (usual care + general information on physical activity).

Chapter 5 presents the protocol of the 4-STEPS trial. The protocol describes in detail the trial rationale, study design and procedures, description of the intervention content and materials, as well as the outcomes assessed.

Two studies (Chapter 6 and 7) present the results of the 4-STEPS implementation. **Chapter 6** reports the post-treatment (3-months) effects of the 4-STEPS intervention on fatigue severity (primary outcome) and impact on daily life, physical activity, health-related quality of life, psychological distress and somatic complaints. Intervention effects at follow-up (12-months) are reported in **Chapter 7**. In addition, this last study examines the mediation effects of the intermediate targets of the intervention (physical activity and use of self-regulatory skills) on medium-term changes in fatigue.

The last chapter (**Chapter 8**) integrates and discusses the findings from the different empirical studies. Directions for future research and practical implications are formulated.

References

1. Torres-Harding, S., Jason, L.A. *What is fatigue? History and epidemiology, in Fatigue as a window to the brain*, Ed. 2005: p. 3-17. MIT Press: Cambridge.
2. Fernandez, A., Martín, A., Martínez, M., Hernandez, F.,..., Giménez, J. *Chronic fatigue syndrome: aetiology, diagnosis and treatment*. BMC Psychiatry, 2009. 9(Suppl 1): S1.
3. Prins, J.B., Van der Meer, J.W.M., Bleijenberg G. *Chronic fatigue syndrome*. Lancet, 2006. 367: 346-355.
4. Fukuda, K., Straus, S., Hickie, I., Sharpe, M., Dobbins, J., Komaroff, A. *The chronic fatigue syndrome: a comprehensive approach to its definition and study*. Annals of Internal Medicine, 1994. 121: 953-9.
5. Sharpe, *M.C. A Report-Chronic Fatigue Syndrome: Guidelines for Research*. Journal of the Royal Society of Medicine, 1991. 84(2): 118-121.
6. Carruthers, B.M., van de Sande, M.I., Meirlier, L.L., Klimas, N.,..., Stevens, S. *Myalgic encephalomyelitis: International Consensus Criteria*. Journal of Internal Medicine, 2011. 270(4): 327-338.
7. Wessely, S. Foreword. *Fatigue as a window to the brain*, 2005: p. x - xvii.
8. Afari, N., Buchwald, D. *Chronic Fatigue Syndrome: A Review*. American Journal of Psychiatry, 2003. 160: 221-236.
9. Harvey, S. Wessely, S. *Chronic fatigue syndrome: identifying zebras amongst the horses*. BMC Medicine, 2009. 7(1): 58.
10. Hardt, J., Buchwald, D., Wilks, D., Sharpe, M., Nix, WA. *Health-related quality of life in patients with chronic fatigue syndrome: an international study*. Journal of Psychosomatic Research, 2001. 51(2): 431-4.
11. Johnson, S.K. *Depression and Fatigue, in Fatigue as a window to the brain*, J. DeLuca, Ed. 2005: p. 157-172. MIT Press: Cambridge.
12. Allen, L.A., Escobar, J.L. *Fatigue and somatization, in Fatigue as a window to the brain*, J. DeLuca, Ed. 2005: p.173-183. MIT Press: Cambridge.
13. Maquet, D., Demoulin, C., Crielaard, J.M. *Chronic fatigue syndrome: a systematic review*. Ann Readapt Med Phys, 2006. 49(6): 337-47.
14. Ranjith, G., *Epidemiology of chronic fatigue syndrome*. Occupational Medicine, 2005. 55(1):13-19.
15. Cho, H.J., Menezes, P.R., Hotopf, M., Bhugra, D., Wessely, S. *Comparative epidemiology of chronic fatigue syndrome in Brazilian and British primary care: prevalence and recognition*. British Journal of

Psychiatry, 2009. 194(2): 117-22.
16. Hickie, I., Davenport, T., Vernon, S.D., Nisenbaum, R.,..., International chronic fatigue study group. *Are chronic fatigue and chronic fatigue syndrome valid clinical entities across countries and health-care settings?* Australian and New Zealand Journal of Psychiatry, 2009. 43(1): 25-35.
17. Skapinakis, P., Lewis, G., Mavreas, V. *Cross-cultural differences in the epidemiology of unexplained fatigue syndromes in primary care*. British Journal of Psychiatry, 2003.
182: 205-9.
18. Cairns, R., Hotpof, M. *Prognosis of chronic fatigue syndrome: a systematic review.* Occupational Medicine, 2005. 55: 20-31.
19. Sabes-Figuera, R., McCrone, P., Hurley, M., King, M., Donaldson, A.N, Ridsdale, R. T*he hidden cost of chronic fatigue to patients and their families.* BMC Health Services Research, 2010. 10(1): 56.
20. Van Houdenhove, B., Luyten, P. *Customizing treatment of chronic fatigue syndrome and fibromyalgia: the role of perpetuating factors*. Psychosomatics, 2008. 49(6): 470-7.
21. Knoop, H., Prins, J.B., Moss-Morris, R., Bleijenberg, G. *The central role of cognitive processes in the perpetuation of chronic fatigue syndrome*. Journal of Psychosomatic Research, 2010. 68(5): 489-94.
22. Moss-Morris, R., *Symptom perceptions, illness beliefs and coping in chronic fatigue syndrome*. Journal of Mental Health, 2005. 14: 223-35.
23. Nijs, J., Wallman, K., Paul, L., *Chronic Fatigue Syndrome, in Exercise and Chronic Disease: An Evidence-Based Approach*, J.M. Saxton, Ed. 2011: p. 322-338- Routledge: New York, USA.
24. Nijs, J., Aelbrechtm S., Meeus, M., Van Oosterwijck, J., Zinzen, E., Clarys, P. *Tired of being inactive: a systematic literature review of physical activity, physiological exercise capacity and muscle strength in patients with chronic fatigue syndrome*. Disability and Rehabilitation, 2011. 33(17-18): 1493-1500.
25. Fulcher, K.Y., White, P.D. *Strength and physiological response to exercise in patients with chronic fatigue syndrome*. Journal of Neurology Neurosurgery and Psychiatry, 2000. 69: 302-307.
26. Clark, L., White, P. *The role of deconditioning and therapeutic exercise in chronic fatigue syndrome (CFS)*. Journal of mental health, 2005. 14(3): 237-252.
27. Nijs, J., Paul, L., Wallman, K. *Chronic fatigue syndrome: an approach combining self-management with graded exercise to avoid exacerbations*. Journal of Rehabilitation Medicine, 2008. 40: 241-247.

28. Black, C., O'Connor, P., McCully, K. *Increased daily physical activity and fatigue symptoms in chronic fatigue syndrome*. Dynamic Medicine, 2005. 4(1): 3.
29. Black, C., McCully, K. *Time course of exercise induced alterations in daily activity in chronic fatigue syndrome*. Dynamic Medicine, 2005. 4(1): 10.
30. Spence, M., Moss-Morris, R., Chalder, *T. The behaviour responses to illness questionnaire (BRIQ): a new predictive measure of medically unexplained symptoms following acute infection*. Psychological Medicine, 2005. 35: 583-593.
31. van der Werf, S.P., Prins, J.B., Vercoulen, J.H., van der Meer, J.W., Bleijenberg, G. *Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment*. Journal of Psychosomatic Research, 2000. 49(5): 373-9.
32. National Institute for Health and Clinical Excelence. NICE clinical guideline 53. Chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy: diagnosis and management of CFS/ME in adults and children, 2007.
33. American College of Sports Medicine. ACSM's *guidelines for exercise testing and prescription*. 8th edition, 2009. Baltimore: Lippincott Williams & Williams.
34. Fulcher, K.Y, White, P.D. *Chronic Fatigue Syndrome: A description of graded exercise treatment*. Physiotherapy, 1998. 84(5): 223-226.
35. Edmonds, L., McGuire, L., Price, J. *Exercise Therapy for Chronic Fatigue Syndrome*. Cochrane Database Systematic Review, 2004. 3: CD003200.
36. Castell, B.D., Kazantsis, N., Moss-Morris, R. *Cognitive Behavioral Therapy and Graded Exercise for Chronic Fatigue Syndrome: A Meta-Analysis*. Clinical Psychology Science and Practice, 2011. 18(4): 311-324.
37. Mallouf, J.M., Thorsteinsson, E.B., Rooke, S.E., Bhullar,N., Schutte, N.S. *Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: A meta-analysis*. Clinical Psychology Review, 2008. 28(5): 736-745.
38. Sharpe, M., Peveler, R., Mayou, R. *The psychological treatment of patients with functional somatic symptoms: A practical guide*. Journal of Psychosomatic Research, 1992. 36(6): 515-529.
39. Bleijenberg, G., Prins, J.B., Bazelmans, E. *Cognitive-behavioral therapies, in Handbook of Chronic Fatigue Syndrome*, L.A. Jason, P.A. Fennell, and R.R. Taylor, Eds. 2003: p. 493–526. Wiley: New Jersey.

40. Price, J., Mitchell, E., Tidy, E., Hunot, V. *Cognitive behaviour therapy for chronic fatigue syndrome in adults*. Cochrane Database Systematic Review, 2008. 3: CD001027.
41. Vos-Vromans, D., Smeets, R., Rijnders, L., Gorrissen, R.,..., Knottnerus, A. *Cognitive behavioural therapy versus multidisciplinary rehabilitation treatment for patients with chronic fatigue syndrome: study protocol for a randomised controlled trial* (FatiGo). Trials, 2012. 13(1): 71.
42. Wallman, K., Morton, A., Goodman, C., Grove, R., Guilfoyle, A. *Randomised controlled trial of graded exercise in chronic fatigue syndrome*. Medical Journal of Australia, 2004. 180(9): 444-448.
43. Wiborg, J.F., Knoop, H., Stulemeijer, M., Prins, J.B., Bleijenberg, G. *How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity*. Psychological Medicine, 2010. 40(08): 1281-1287
44. Moss-Morris, R., Sharon, C., Tobinm R., Baldi, J.C. *A randomized controlled graded exercise trail for chronic fatigue syndrome: outcomes and mechanisms of change*. Journal of Health Psychology, 2005. 10(2): 245-259.
45. Knoop, H., Van der Meer, J., Bleijenberg, G. *Guided self-instructions for people with chronic fatigue syndrome: a randomised controlled trial*. British Journal of Psychiatry, 2008. 190: 340 - 341.
46. Tummers, M., Knoop, H., van Dam, A., Bleijenbeg , G. *Implementing a minimal intervention for chronic fatigue syndrome in a mental health centre: a randomized controlled trial*. Psychological Medicine, 2012. 42(10): 2205-2215.
47. Powell, P., Bental, R.P., Nye, F.J., Edwards, R.H.T. *Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome*. BMJ, 2001. 322: 387.
48. Chambers, D., Bagnall, A.M., Hempel, S., Forbes, C. *Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis: an updated systematic review*. Journal of Royal Society of Medicine, 2006. 99(10): 506-20.
49. Maes, S., Karoly, P. Self-regulation assessment and intervention in physical health and illness: a Review. Applied Psychology: International Review, 2005. 54(29): 267-299.
50. de Ridder, D., de Witt, J. *Self-regulation in Health Behavior: Concepts, Theories, and Central Issues*, in Self-regulation in health behavior, D. de Ridder and J. de Witt, Eds. 2006: p. 1-23. John Wiley & sons.

51. Bandura, A., *The Primacy of Self-Regulation in Health Promotion*. Applied Psychology, 2005. 54(2): 245-254.
52. Carver, C.S. and Scheier, M.F. *On the self-regulation of behavior*. 1998, New York: University Press.
53. Deci, E.L. and R.M. Ryan, *The 'what' and 'why' of goal pursuits: Human needs and the self-determination of behavior*. Psychological Inquiry, 2000. 11: 227-268.
54. De Gucht, V. and S. Maes, *Explaining medically unexplained symptoms: toward a multidimensional theory-based approach to somatisation*. Journal of Psychosomatic Research, 2006. 60: 349-35.
55. Deary, V. *A precarious balance: using a self-regulation model to conceptualize and treat chronic fatigue syndrome*. British Journal of Health Psychology, 2008. 13: 231-236.
56. Sniehotta, F.F., U. Scholz, and R. Schwarzer, *Bridging the intention–behaviour gap: Planning, self-efficacy, and action control in the adoption and maintenance of physical exercise*. Psychology & Health, 2005. 20(2):143-160.
57. Janssen, V., de Gucht, van Exel, H., Maes, S. *A self-regulation lifestyle program for post-cardiac rehabilitation patients has long-term effects on exercise adherence*. Journal of Behavioral Medicine, 2014. 37(2): 308-21.
58. Clark, N.M., et al., *A randomized trial of a self-regulation intervention for women with asthma*. Chest, 2007. 132(1): 88-97.
59. Knittle, K., de Gucht, V, Hurkmans, E., Peeter, A.,...Vliet Vlieland, T. *Targeting motivation and self-regulation to increase physical activity among patients with rheumatoid arthritis: a randomised controlled trial*. Clinical Rheumatology, 2013: 1-8.
60. Michie, S., et al., *Effective techniques in healthy eating and physical activity interventions: A meta-regression*. Health Psychology, 2009. 28(6): 690-701.
61. Jansen, V., de Gucht, V., Dusseldorp, E., Maes, S. *Lifestyle modification programmes for patients with coronary heart disease: A systematic review and meta-analysis of randomized controlled trials*. European Journal of Preventive Cardiology, 2013. 20(4): 620-640.
62. Knittle, K., S. Maes, and V. de Gucht, *Psychological interventions for rheumatoid arthritis: Examining the role of self-regulation with a systematic review and meta-analysis of randomized controlled trials*. Arthritis Care & Research, 2010. 62(10): 1460-1472.
63. Huisman, S.D., De Gucht, V., Dusseldorp, E., Maes, S. *The Effect of*

Weight Reduction Interventions for Persons With Type 2 Diabetes: A Meta-analysis From a Self-regulation Perspective. The Diabetes Educator, 2009. 35(5): 818-835.
64. Vercoulen, J., M. Alberets, and G. Bleijenberg, *De Checklist Individual Strenght* (CIS). Gedragstherapie, 1999. 32: p. 31-36.
65. Vercoulen, J.H., Swanink, C.M., Fennis, J.F., Galama J.M., van der Meer, J.W., Bleijenberg, G. *Prognosis in chronic fatigue syndrome: A prospective study on the natural course*. Journal of Neurology, Neurosurgery, and Psychiatry, 1996. 60: p. 489-94.

02

Psychometric properties of the Portuguese Version of the Checklist of Individual Strength (CIS20-P)

Manuscript published
M. Marques, V. De Gucht, M.J. Gouveia, A. Cordeiro, I. Leal & S. Maes (2013). Psychometric properties of the Portuguese Version of the Checklist of Individual Strength (CIS20-P)
Psychology, Community & Health, 2(1):11-19.

Abstract

Aim: The Checklist of Individual Strength (CIS20) is a well validated measure of fatigue severity, which has been adapted in several languages. As Portuguese is one of the most widely spoken languages in the world it is important to have a Portuguese adaptation of the CIS20.
Method: Four hundred and thirty healthy Portuguese adults and 89 patients with chronic fatigue (CF) filled out the Portuguese version of the CIS20 (CIS20-P). The CF patients and a subsample of the healthy adults also filled out the SF-12v2 assessing health-related quality of life.
Results: The CIS20 four-factor structure was confirmed (subjective experience of fatigue, concentration, motivation and physical activity scales). In general, internal consistency estimates were satisfactory, with the exception of the motivation scale. Moreover, a higher degree of fatigue severity was significantly associated with lower vitality and physical and psychological health-related quality of life.
Conclusion: Our results indicate that the CIS20-P is a reliable and valid measure of fatigue severity. Future studies should establish Portuguese cut-off points for (sub)clinical levels of fatigue.

Keywords: chronic fatigue, Checklist of Individual Strength (CIS20), Portuguese, psychometric properties

Introduction

Fatigue is a common symptom reported worldwide, that can vary in length (acute or chronic) and severity (Torres-Harding & Jason, 2005). Persistent and severe fatigue can lead to functional impairment (Beurskens, Bültmann, Kant, Vercoulen, Bleijenberg, & Swaen, 2000). Fatigue is present in several clinical conditions (e.g. cancer) and is called unexplained or idiopathic chronic fatigue (ICF) if it lasts for at least six months, is debilitating and is not explained by an organic disease (Fukuda, Straus, Hickie, Sharpe, Dobbins, & Komaroff, 1994). If additional somatic symptoms established by the Centers for Disease Control and Prevention (CDC) are present, it is classified as Chronic Fatigue Syndrome (CFS) (Fukuda et al., 1994).

Due to its subjective nature, fatigue is difficult to define and measure (Wessely, 2005). Several self-report unidimensional and multidimensional measures of fatigue have been developed in the past two decades. Multidimensional assessment has the advantage of providing more detail on fatigue dimensions, such as physical and mental fatigue (Christodolou, 2005; Dittner, Wessely, & Brown, 2004). The Checklist of Individual Strength (CIS-20) developed by Vercoulen and colleagues (Vercoulen, Alberets, & Bleijenberg, 1999; Vercoulen et al., 1994) is a well validated and widely used multidimensional self-report measure assessing subjective experience of fatigue, concentration, motivation and physical activity level (for a detailed review on fatigue measurement see Christodolou, 2005; Dittner et al., 2004).

The CIS20 was developed for CFS patients and is extensively used within this population (e.g. Knoop, Van der Meer, & Bleijenberg, 2008; Vercoulen et al., 1996a), within other clinical conditions (e.g. Ergin & Yildirim, 2012; Vercoulen et al., 1996b) as well as within healthy and working groups (e.g. Beurskens et al., 2000; Bültmann, Vries, Beurskens, Bleijenberg, & Vercoulen, 2000). The CIS20 was demonstrated to have good internal consistency and validity across studies. In addition, it has been shown to discriminate between non-fatigued and fatigued groups (e.g. Beurskens et al., 2000; Bültmann et al., 2000) and cut-off points for clinical levels of

fatigue have been developed (Bültmann et al., 2000; De Vree et al., 2002). The CIS20 has been adapted in several languages, including Japanese (Aratake et al., 2007), Polish (Makowiec-Dabrowska & Koszada-Wlodarczyk, 2006) and Turkish (Ergin & Yildirim, 2012), presenting good cross-cultural reliability and validity.

Since Portuguese is one of the most widely spoken languages in the world the development of a Portuguese version of the CIS20 is needed. Therefore, the aim of this study is to examine the reliability and validity of the CIS20-P across two different groups: a healthy population and a population suffering from CF.

Method

Participants

This research included two samples: 430 healthy adults and 89 CF patients. Table 1 presents the demographic characteristics of the samples. In both groups, inclusion criteria were: 18 - 65 years old; fluency in Portuguese and capacity to provide an informed consent. In the CF group, participants were also required to meet the CDC criteria for ICF/CFS (Fukuda et al., 1994). Exclusion criteria were: the presence of a concurrent somatic condition that could explain the fatigue symptoms and/or the presence of a severe psychiatric disorder.

Measures

Checklist of Individual Strength (CIS20-P)

The CIS20 items represent four dimensions of fatigue: Subjective experience of fatigue (e.g. "I feel weak" – eight items), Concentration (e.g. "I have trouble concentrating"– five items), Motivation (e.g. "I feel no desire to do anything" – four items) and Physical activity (e.g. "I have a low output" – three items). Respondents indicate, on a seven-point Likert scale ranging from "Yes, that is true" to "No, that is not true", the extent to which each statement applied to them in the past two weeks. Scores are calculated by adding up the results from the items of each scale. Higher scores indicate higher levels of subjective experience of fatigue (ranging from 8 to 56), reduced concentration (5-35),

reduced motivation (4-28) and lower levels of physical activity (3-21). Furthermore, a total CIS20 score (fatigue severity) can be calculated by adding up the scores from each dimension (20 -140).

Procedure

Two different procedures were followed for each group. The CF participants were recruited through several Portuguese health care institutions and the Portuguese Fibromyalgia and Chronic Fatigue Patient Association. Questionnaires were filled out during individual face-to-face sessions with the principal investigator, as part of a larger study on CF (Marques, De Gucht, Maes, & Leal, 2012). Participants from the healthy group are a convenience sample (recruited in organizational and academic settings). Participants were asked to complete the questionnaires and return them by prepaid mail or email. For both samples, informed consent was obtained and confidentiality of the data was guaranteed by the research team.

Cross Cultural Translation of the CIS20

For the Portuguese adaptation of the CIS20, the English version presented by Beurskens (Beurskens et al., 2000) was used following the recommended procedure translate-translate back (Hill & Hill, 2005).

Data Analysis

Confirmatory Factor Analysis (*CFA*) (Arbuckle, 2005) using a maximum likelihood (*ML*) estimation method was used to test the validity of the four-factor structure of the CIS20-P in both the healthy and CF samples. Comparative Fit Index (*CFI*), Nonnormed Fit Index (*NNFI*), Goodness of Fit Index (*GFI*), Root-Mean Square Error of Approximation (*RMSEA*) fit indices and χ^2 statistics were used to determine the adequacy of the models. A *CFI* >.90, *GFI* >.90, *NNFI*>.90 and *RMSEA*<.05 with 90% *CI* < .10 are acceptable indices of fit for the model and χ^2/df <5 is considered to be reasonable (Byrne, 2001). Multivariate normal distributions of the responses were examined by means of the standardized Mardia's coefficient (Mardia, 1974). Cronbach's coefficient alphas were calculated for internal consistency. To assess the discriminant validity of the

CIS20-P, samples were matched on age, gender and educational level (healthy sample: *n*= 157; CF sample: *n*=89). There were no significant differences between both groups on these demographic variables. In order to explore differences on the CIS20, independent samples t-tests were conducted. The convergent and concurrent validity of the CIS20-P was analyzed using bivariate Pearson correlation coefficients with the Vitality scale and Physical and Psychological health-related quality of life dimensions (HRQoL) of the SF-12v2 (Ware, Kosinski, Turner-Bowker, & Gandek, 2002), that were completed by the CF population (*n*=89) and a subgroup of the healthy sample (*n* = 176).

All analyses were performed with SPSS v.19 and AMOS v.20 statistical packages.

Results

Descriptive Statistics and Reliability of the CIS20-P

Tables 2 and 3 present descriptive data and internal consistency data for each CIS20-P scale in the healthy and CF sample, respectively. In the healthy group, internal consistency coefficients were satisfactory and above $\alpha = .78$ for the Subjective experience of fatigue, Concentration and Physical activity scales. Slightly inferior Cronbach's alphas were observed in the CF sample (> .69). In both groups, the Motivation scale proved to have poor internal consistency ($\alpha = .51$ for the healthy group and $\alpha = .58$ for the CF group, respectively). Yet, all items contributed to the internal consistency of this scale.

Factorial validity of the CIS20-P

Multivariate kurtosis was observed in the healthy *(Kurtosis/c.r.* = 2.86) and CF samples (*Kurtosis/c.r.* = 6.29). Nevertheless, the maximum likelihood estimation method used in *CFA* is robust even in the presence of a non-normal distribution of the data (Maroco, 2010).

The CFA adjustment fit indices of the four-structure model were reasonable for the healthy sample (χ^2/df = 4.731; *CFI* = .85; *NNFI* = .82; *GFI* = .82; *RMSEA* = .093; 90% *CI* [.087 - .100]). All items loaded

significantly on their respective factor (see Table 2). In the CF sample, the adjustment fit indices of the model were poorer (χ^2/df = 1.739; *CFI* = .76, *NNFI* = .72; *GFI* = .75; *RMSEA* = .092, 90%; *CI* [.074 - .107]). The path coefficients were smaller in the CF group (Table 3), in which items four ("Physically I feel exhausted" - Subjective experience of fatigue scale) and five ("I feel like doing all kinds of nice things" - Motivation scale) had very low loadings on their respective factor (.13 and .15, respectively).

The inter-correlations among the CIS20-P scales ranged from .33 (Subjective fatigue and Concentration) to .80 (Physical activity and Concentration). The correlation coefficients were equivalent in both groups, with the exception of the relation between Concentration and Subjective experience of fatigue, which was higher in the healthy population (.62).

Discriminant Validity of the CIS20-P

The results presented in Table 4 show that in comparison with a matched healthy group, the CF participants scored systematically higher on all CIS20-P dimensions. All differences were statistically significant ($p < .001$).

Convergent and Concurrent Validity of the CIS20-P

The Pearson correlation coefficients between the total CIS20-P score and the SF-12v2 indicators (Vitality, Physical and Psychological HRQoL) are presented in Table 5. All correlations were negative and statistically significant ($p < .01$) in both groups. The largest correlations emerged in the healthy sub-sample.

Discussion

This study aimed at analyzing the reliability and validity of the Portuguese Version of the CIS20 in a healthy adult population and a sample of CF patients.

Overall, the CIS20-P dimensions and the total scale presented satisfactory internal consistency estimates, similar to those found in previous validation studies (Aratake et al., 2007; Makowiec-Dabrowska & Koszada-Wlodarczyk, 2006). For the CF population,

the Cronbach's alphas within the present study were lower than those presented in the Dutch studies (Dittner et al., 2004). In addition, the motivation scale presented a very low internal consistency in both samples, which is in line with the findings of the Polish version of the CIS20 (α = .61) (Makowiec-Dabrowska & Koszada-Wlodarczyk, 2006). More in particular, item five ("I feel like doing all kinds of nice things") presented a lower correlation with the factor motivation and a lower factor loading in comparison to the other items. One explanation may be that there are cross-cultural differences in the expression of reduced motivation. Future studies should further explore this hypothesis and, eventually, changes should be made to the Portuguese version of the motivation scale (e.g. by adding new items).

Although we found support for the four-factor structure of the CIS-20P in both samples, the adjustment indices of fit were worse in the CF sample. The small size of this group (n = 89) may partly explain this difference. In addition, differences in the procedure used for data collection in each sample, may also have contributed to the differences found. Few studies have analyzed the factorial structure of the CIS20. The Japanese version presents similar factorial validity estimates (Aratake et al., 2007).

The CIS20-P proves to discriminate well between a matched healthy and the CF sample. CF patients demonstrated significantly higher levels of subjective fatigue, lower motivation, lower concentration, reduced physical activity and a worse fatigue severity, which is in line with previous studies (Beurskens et al., 2000; Bültmann et al., 2000; Vercoulen et al., 1996b).

Finally, the convergent and concurrent validity of the CIS20-P was examined in both samples. Higher fatigue severity was significantly associated with lower vitality and physical and psychological HRQoL, in both groups. These results confirm previous research (Ergin & Yildirim, 2012).

We recommend that future studies explore other psychometric properties of the CIS20-P (e.g. sensitivity to change), establish Portuguese cut-off points for (sub)clinical levels of fatigue, and examine the discriminant validity of the CIS20-P in other clinical (e.g. cancer, diabetes) and non-clinical samples (e.g. organizational settings). In addition, validation studies should be conducted in

other Portuguese speaking countries that are culturally different (e.g. Brazil).

Our findings indicate that the CIS20-P is a useful tool to assess fatigue severity.

Acknowledgements

This study was partially funded by the Portuguese Foundation for Science and Technology with a grant to the first author (SFRH/BD/47579/2008).

The authors would like to thank the patients, the medical doctors from the Health Care Institutions, the volunteers from the Patients Associations and the general population that participated in this research.

References

Aratake, Y., Tanaka, K., Wada, K., Watanabe, M., Katoh, N., Sakata, Y., & Aizawa, Y. (2007). Development of Japanese version of the Checklist Individual Strength questionnaire in a working population. *Journal of Occupational Health Psychology*, 49, 453-460.

Arbuckle, J. (2005). *Amos 6.0 User's guide*. Chicago, IL:SPSS, Inc.

Beurskens, A., Bültmann, U., Kant, I., Vercoulen, J., Bleijenberg, G., & Swaen, G. (2000). Fatigue among working people: validity of a questionnaire measure. *Occupational and Environmental Medicine, 57*, 353-357. doi:10.1136/oem.57.5.353

Bültmann, U., Vries, M., Beurskens, A., Bleijenberg, G., & Vercoulen, J. (2000). Measurement of prolonged fatigue in the working population: determination of a cutoff point for the Checklist Individual Strength. *Journal of Occupational Health Psychology, 5*(4), 411-416.

Byrne, B.M. (2001). *Structural equation modeling with AMOS. Basic concepts, applications, and programming.* NJ: Lawrence Erlbaum Associates, Publishers.

Christodolou, C. (2005). The assessment and measurement of fatigue. In DeLuca, J. (Ed.), *Fatigue as a window to the brain*. (pp. 19-35), Cambridge: MIT Press

De Vree, B., Van der Werf, S., Prins, J., Bazlmans, E., Vercoulen, J., & Servaes, P. (2002). Meetinstrumenten bij chronische vermoeidheid. *Gedragstherapie, 35*, 157-164.

Dittner, A.J., Wessely, S.C., & Brown, R.G. (2004). The assessment of fatigue: a practical guide for clinicians and researchers. *Journal of Psychosomatic Research, 56*(2), 157-170. doi: 10.1016/S0022-3999(03)00371-4.

Ergin, G., & Yildirim, Y. (2012). A validity and reliability study of the Turkish Checklist of Individual Strength (CIS) questionnaire in musculoskeletal physical therapy patients. *Physiotherapy: Theory and Practice, 28,* 624-632. doi:10.3109/09593985.2011.654321.

Fukuda K., Straus S.E., Hickie I., Sharpe M.C., Dobbins J.G., & Komaroff A. (1994). The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of Internal Medicine, 121*, 953-959.

Hill, M., & Hill, A. (2005). *Investigação por questionário*. Lisboa: Edições Sílabo.

Knoop, H., Van der Meer, J.W., & Bleijenberg, G. (2008). Guided self-instructions for people with chronic fatigue syndrome: a randomised controlled trial. *The British Journal of Psychiatry, 193*, 340-341. doi: 10.1192/bjp.bp.108.051292.

Makowiec-Dabrowska, T., & Koszada-Wlodarczyk, W. (2006). The CIS20R questionnaire and its suitability for prolonged fatigue studies. *Medycyna Pracy, 57(*4), 335-345.

Mardia, K.V. (1974). Applications of some measures of multivariate skewness and kurtosis in testing normality and robustness studies. *Sankhyã: The Indian Journal of Statistics, Series B*(36), 115-128.

Maroco, J. (2010). *Análise de equações estruturais: fundamentos teóricos, software & aplicações*. Pêro Pinheiro: ReportNumber.

Marques, M., De Gucht, V., Maes, S., & Leal, I. (2012). Protocol for the "Four steps to control your fatigue (4-STEPS)" randomised controlled trial: a self-regulation based physical activity intervention for patients with unexplained chronic fatigue. *BMC Public Health, 12*, 202. (Highly accessed). doi: 10.1186/1471-2458-12-202

Torres-Harding, S., & Jason, L. A. (2005). What is fatigue? History and epidemiology. In DeLuca, J. (Ed.), *Fatigue as a window to the brain* (pp. 3-17). Cambridge: MIT Press.

Vercoulen, J.H.M.M., Swanink, C.M.A., Fennis, J.F.M., Galama, J.M.D., Van der Meer J.W.M., & Bleijenberg, G. (1994). Dimensional assessment of chronic fatigue syndrome. *Journal of Psychosomatic Research, 38*(5), 383-392.

Vercoulen, J., Swanink, C., Fennis, J., Galama, J., Meer, J., & Bleijenberg, G. (1996a). Prognosis in chronic fatigue syndrome: a prospective study on the natural course. *Journal of Neurology, Neurosurgery & Psychiatry, 60,* 489-494. doi: 10.1136/jnnp.60.5.489

Vercoulen, J., Hommes, O., Swanink, C., Jogen, P., Fennis, J., Galama, J., ... Bleijenberg, G. (1996). The measurement of fatigue in patients with multiple sclerosis: a multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. *Archives of Neurology*, 53(7), 642-649.

Vercoulen, J.H.M.M., Alberets, M., & Bleijenberg, G. (1999) De Checklist Individual Strength (CIS). *Gedragstherapie, 32,* 31-36.

Ware, J.E., Kosinski, M., Turner-Bowker, D.M., & Gandek, B. (2002). *How to score version 2 of the SF-12® Health Survey*. Lincoln, RI: Quality Metric Incorporated.

Wessely, S. (2005). Foreword. In DeLuca, J. (Ed.), *Fatigue as a window to the brain*. (pp. x-xvii), Cambridge: MIT Press.

Table 1 Demographic characteristics of the healthy and CF samples

	Healthy (N=430)	**Healthy Subsample** [a] (N=157)	**CF** (N=89)
Female patients (%)	74.4	93	97.8
Age, years (Mean±SD)	36.17 ± 12.12	48.22±9.37	47.55 ± 10.88
Educational level (%)			
Lower education	7.7	17.7	27
Higher education	92.3	82.3	73

[a] *Matched healthy subsample for discriminant validity analysis.*

Table 2 Descriptives, Chronbach's alphas and factor loadings for the Portuguese version of the CIS-20P for the healthy population (N=430)

Items/Scales	Min-Max	Mean	SD	Item total correlation	α	Factor Loadings[a]
Subjective fatigue	*8-56*	*28.97*	*12.09*		*.90*	
CIS1	1-7	4.47	2.11	.66		.66
CIS4	1-7	3.34	2.01	.66		.66
CIS6	1-7	3.83	1.90	.75		.82
CIS9	1-7	2.94	1.92	.70		.72
CIS12	1-7	3.77	1.90	.57		.59
CIS14	1-7	3.59	2.13	.71		.78
CIS16	1-7	3.10	1.93	.64		.68
CIS20	1-7	3.99	2.05	.73		.81
Concentration	*5-35*	*15.55*	*7.23*		*.82*	
CIS3	1-7	3.47	2.13	.44		.42
CIS8	1-7	2.88	1.68	.72		.88
CIS11	1-7	2.96	1.76	.74		.90
CIS13	1-7	3.01	1.87	.68		.74
CIS19	1-7	3.28	2.02	.58		.60
Motivation	*4-25*	*10.81*	*4.39*		*.51*	
CIS2	1-7	3.63	1.88	.33		.47
CIS5	1-7	1.68	1.25	.29		.31
CIS15	1-7	2.90	1.87	.29		.35
CIS18	1-7	2.64	1.91	.34		.63
Physical activity	3-21	7.66	4.19		*.78*	
CIS7	1-7	2.64	1.73	.59		.67
CIS10	1-7	2.54	1.68	.61		.74
CIS17	1-7	2.52	1.67	.65		.79
CIS-20P total	*21-122*	*62.98*	*22.25*		*.91*	

[a]*Obtained from the Confirmatory Factor Analysis*

Table 3 Descriptives, Chronbach's alphas and factor loadings for the Portuguese version of the CIS-20 for the CF group (N=89)

Items/Scales	Min-Max	Mean	SD	Item total correlation	α	Factor Loadings[a]
Subjective fatigue	*29-56*	*46.57*	*6.90*		*.69*	
CIS1	3-7	6.49	1.00	.37		.24
CIS4	1-7	5.52	1.77	.29		.13
CIS6	2-7	5.84	1.42	.54		.89
CIS9	1-7	5.34	1.82	.34		.27
CIS12	1-7	5.72	1.73	.25		.27
CIS14	1-7	5.43	1.64	.45		.46
CIS16	2-7	6.22	1.24	.45		.52
CIS20	1-7	6.01	1.46	.48		.78
Concentration	*5-35*	*25.53*	*6.92*		*.80*	
CIS3	1-7	5.17	2.05	.50		.54
CIS8	1-7	4.58	1.82	.58		.70
CIS11	1-7	5.26	1.82	.67		.78
CIS13	1-7	5.28	1.85	.53		.64
CIS19	1-7	5.24	1.94	.50		.60
Motivation	*4-27*	*15.11*	*4.96*		*.58*	
CIS2	1-7	5.25	1.88	.41		.69
CIS5	1-6	2.02	1.45	.33		.15
CIS15	1-7	3.45	2.09	.40		.36
CIS18	1-7	4.39	1.95	.36		.62
Physical activity	*3-21*	*14.11*	*5.02*		*.73*	
CIS7	1-7	4.21	2.25	ww.46		.61
CIS10	1-7	5.02	1.99	.56		.70
CIS17	1-7	4.88	1.98	.65		.82
CIS-20P total	*54-129*	*101.33*	*17.74*		*.84*	

[a]*Obtained from the Confirmatory Factor Analysis*

Table 4 Descriptives and comparison (independent t-tests) of the CIS-20P total and scales for the healthy and CF sample

CIS-20P dimensions	**Healthy** (N=157)	**CF** (N=89)	**Test for differences** *(t)*
Subjective fatigue	25.38± 11.67	46.57±6.90	-17.89*
Concentration	14.27± 7.15	25.53±6.92	-11.92*
Motivation	10.87 ±4.98	15.11± 4.96	-6.52*
Physical activity	7.32± 4.44	14.11±5.02	-11.19*
CIS-20P total	57.84± 22.75	101.33± 17.74	-16.69*

*Note. Values are the mean ± SD. *p<0.001*

Table 5 Correlations (Pearson) between fatigue severity (total CIS20-P) and Vitality, Physical and Psychological HrQoL in the healthy and Chronic Fatigue sample

SF12v2 dimensions	**Total CIS20-P Healthy** (N=176)	**Total CIS20-P CF** (N=89)
Vitality	-.71*	-.29*
Physical HRQoL	-.63*	-40*
Psychological HRQoL	-.77*	-.56*

**p <0 .01*

03

A cross-cultural perspective on psychological determinants of chronic fatigue syndrome: A comparison between a Portuguese and a Dutch patient sample

Manuscript published
M. Marques, V. De Gucht, I. Leal & S. Maes (2013). A Cross-cultural perspective on psychological determinants of Chronic Fatigue Syndrome: A comparison between a Portuguese and a Dutch patient sample. International Journal of Behavioral Medicine, 20(2): 229-238. (*Sp. Issue on Functional Somatic Syndromes*).

Abstract

Background: Few studies focus on cross-cultural differences in Chronic Fatigue Syndrome (CFS).
Purpose: This study aimed to (1) compare fatigue severity and impairment, somatic complaints, psychological distress and quality of life (QoL) in a population of Portuguese and Dutch patients, (2) explore the differential contribution of behavioral and cognitive determinants of fatigue severity; and (3) investigate the relation between fatigue severity and somatic complaints on the one hand and QoL on the other in both populations.
Methods: Eighty-five female patients from Portugal (Mean age= 47.54) and 167 female CFS patients from the Netherlands (Mean age = 44.93) participated in the study. All participants were surveyed for demographic and clinical characteristics, fatigue severity, somatic symptoms, psychological distress, (physical and psychological) QoL, physical activity, behavior regulation patterns and illness representations.
Results: Cross-cultural differences were found in relation to working status, duration of fatigue symptoms, psychological distress, somatic complaints and psychological QoL. Although behavioral characteristics and illness representations were significantly associated with fatigue severity in both Portuguese and Dutch patients, there were important differences in the determinants of CFS. Moreover, higher levels of fatigue and severity of other somatic complaints were related to poor QoL.
Conclusions: These findings show cross-cultural similarities and differences in clinical characteristics and psychological determinants of CFS that are important in view of diagnosis and treatment.

Keywords: Chronic Fatigue Syndrome; fatigue severity; psychological determinants; cross-cultural.

Introduction

Somatic symptoms, such as fatigue, are an important reason for doctor visits [1, 2] and it is estimated that these symptoms remain medically unexplained in about one third of the cases [1]. Usually, fatigue is explained by life circumstances and is transitory, but for some, fatigue symptoms are indeed medically unexplained, can be severe and become chronic, resulting in functional and social impairment (e.g. inability to work), high use of health care resources and lower Quality of Life (QoL) [2-4]. According to the Centers for Disease Control and Prevention (CDC) fatigue is classified as Chronic Fatigue Syndrome (CFS) when it lasts for at least six months, is not alleviated by rest, is debilitating, results in a significant reduction of daily activities, cannot be explained by an organic disease and is accompanied by four or more of the following symptoms: unrefreshing sleep, lengthy malaise after exertion (lasting for over 24 hours), impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain without swelling or redness and headaches of a new type or severity [5].

Co-morbidity between CFS and psychological distress (depression and anxiety) was found in several studies, although the relationship remains unclear [6-8]. Some prospective studies found the occurrence of psychiatric disorders during adulthood to be associated with later CFS [9, 10]. Other studies suggest that the high rates of psychological distress in CFS patients may be due to a common negative affective reaction to a chronic health problem [6], to disability associated with fatigue [7], to difficulties in the diagnosis of CFS [8], or as a result of the lack of legitimization of the disease by medical doctors [8], among other explanations. Patients with CFS also experience a great number and higher severity of other somatic complaints [4, 11]. Several studies indicate that these patients are hypersensitive to somatic sensations, which can lead to a worsening and increase of the number of symptoms perceived [6, 12, 13].

A psychological perspective on CFS can provide a better understanding of the cognitive and behavioral factors associated with the onset and perpetuation of unexplained fatigue [2, 6]. More

specifically, patients' illness representations and coping strategies can contribute to the worsening and perpetuating of fatigue [6, 13, 14]. Patients with CFS tend to believe that their illness has severe consequences, will last for a long period of time (timeline) and expect many associated symptoms [6, 13, 15]. A prospective study revealed that perceived consequences, timeline, uncontrollability and emotional response predicted worsening and maintenance of chronic fatigue [16]. Patients who belief that they suffer from a severe illness, that their CFS is out of control or incurable and will lead to adverse consequences, usually develop passive ways of coping with their illness leading to high disability and psychological distress [2, 13, 17]. In relation to behavior regulation (coping) it has been suggested that CFS patients tend to adopt a "boom and bust pattern" (also called "All-or-nothing behavior") or a limiting behavior pattern to deal with their illness [13, 16]. All-or-nothing behavior refers to the systematic alternation between periods of excessive activity (when feeling good), and, as a consequence of that, feeling extremely fatigued and having to rest for longer periods of time [13, 18]. Limiting behavior refers to the excessive resting and inactivity, which can be associated with patient complaints related to exercise intolerance and post-exertional malaise. Patients' perceptions and expectations related to symptom exacerbation as a consequence of exercise can explain the reduced levels of physical activity found in these patients [6]. At the same time, lack of physical activity and excessive resting are factors that can result in physical deconditioning which, in turn, might perpetuate fatigue and physical disability [19]. The importance of identifying and understanding the specific cognitive and behavioral determinants of CFS is reinforced by the promising results of CBT and graded exercise approaches in CFS management [20, 21].

CFS is considered to be a heterogeneous clinical condition. Patients may present with different levels of (mental and physical) fatigue severity, psychological distress, additional somatic symptoms and different levels of impairment and disability [3, 6]. For this reason, fatigue severity and related somatic symptoms, psychological distress and QoL, may vary between countries and cultures [22, 23]. Most studies on the prevalence and clinical characteristics of CFS have been conducted in North-West

Europe, North America and Oceania [23], while there are very few international studies that compare patient populations from different countries [3, 22, 23]. Hickie and colleagues [22] explored CFS worldwide, using existing data from different cultures. Results revealed a five-factor model of symptoms (musculoskeletal pain and prolonged fatigue, neurocognitive difficulties, sleep disturbance, inflammation and mood disturbance), confirming that CFS is indeed a universal disease. Another study on health related QoL conducted with US, UK and German CFS patients, showed that these patients reported a lower QoL in all countries [3]. In a study comparing the prevalence and recognition of CFS in primary health care services between Brazil and England [23], the prevalence of CFS appeared to be similar in both countries, but there were differences in the recognition of CFS as a discrete disorder leading to a lower number of diagnosed patients in Brazil.

Likewise, cross-cultural research on the psychological determinants of CFS, such as behavioral (e.g. physical activity) and cognitive (e.g. illness representations) factors is lacking, although this type of research can contribute to the cultural adaptation of existing CFS models and the development of tailored treatment strategies. For this reason, we conducted a comparative study between two economically and culturally distinct countries: Portugal (a Southern European country) and the Netherlands (a North-Western European country), as we expected differences in clinical characteristics and determinants of CFS. Available data reveal differences in psychological distress and physical activity between the two populations [24, 25].

This is an exploratory study aiming at: (1) comparing fatigue impairment and severity, somatic complaints, psychological distress and (physical and psychological) QoL in Portuguese and Dutch CFS patients (2) exploring differential effects of behavioral (physical activity and behavior regulation patterns) and cognitive factors (illness representations) on fatigue severity in the study populations and (3) examining the contribution of fatigue severity and somatic complaints to (physical and psychological) QoL in Portuguese and Dutch CFS patients.

Method

Participants and Procedures

This cross-sectional study included participants from two countries: Portugal and the Netherlands. In both cases, inclusion criteria were: meeting the CDC criteria for CFS [5]; being at least 18 years old; being fluent in Portuguese/Dutch; and having the capacity to provide an informed consent. Exclusion criteria were similar for both samples: presence of a concurrent somatic condition that could explain fatigue symptoms and/or presence of a severe psychiatric disorder (according to the CDC criteria for exclusionary medical and psychiatric conditions). Table 1 presents the demographic and clinical characteristics of the samples.

Participants from Portugal were recruited via various health care institutions and from the national Chronic Fatigue Syndrome and Fibromyalgia Patients Association. CFS patients from the health care institutions were referred by their medical doctor, based on the inclusion and exclusion criteria for the study. Patients from the Patients Association had a clinical diagnosis of unexplained chronic fatigue. Patients were approached by the research team to complete the questionnaires. Participants from the Netherlands were recruited through the national Chronic Fatigue Syndrome Patients Association. All Dutch patients were medically diagnosed as having CFS. The members of this association were invited via email by the patient association to complete the questionnaire. For both samples, informed consent was obtained and confidentiality of the data was guaranteed by the research team. Furthermore, the inclusion and exclusion criteria were checked by the research team, using self-report measures (CDC checklist of CFS symptoms; presence and name of chronic disease; presence and name of psychiatric disorder).

For this study patients from Portugal and the Netherlands were matched on age, gender (only female patients were included) and diagnosis (only patients fulfilling the CDC criteria for CFS were included).

Measures

Patient characteristics

Socio-demographic characteristics include age, gender, education and employment status (Table 1). Clinical information was gathered using 4 indicators: (1) presence of persistent fatigue, (2) duration of fatigue symptoms (months), (3) number of doctor visits in the previous 6 months, and (4) a CDC based symptom checklist for CFS. The checklist includes the 8 major symptoms of CFS defined by the CDC criteria [5]. Respondents are asked to rate using a dichotomous scale (Yes/No) whether they experienced the symptoms for the last 6 months. To be diagnosed with CFS patients need to have a complaint of persistent unexplained fatigue for at least 6 months and have at least 4 of the major CFS symptoms listed by the CDC [5].

Fatigue Severity

The Checklist of Individual Strength (CIS-20R) was used to assess fatigue levels [26]. The CIS-20R is a 20 item self-report questionnaire that assesses four dimensions of fatigue: *subjective experience of fatigue*, *lack of concentration*, *lack of motivation* and *activity reduction*. Items are rated on a 7-point Likert scale ranging from "Yes, that is true" to "No, that is not true". A total CIS-20R score (fatigue severity), ranging from 20 to 140, can be calculated by adding the scores from each dimension. Higher scores indicate higher levels of fatigue severity. For the purpose of this study only the total fatigue severity score and the subjective experience of fatigue dimension were used. A cut-off point of 35 for subjective experience of fatigue [27] is used to define clinical levels of fatigue. The CIS-20R is a well validated and reliable measure for CFS patients [26]. Data on the Portuguese version of the CIS-20R reveal good reliability of the dimensions subjective experience of fatigue and total fatigue severity ($\alpha = 0.89$ and $\alpha = 0.90$, respectively) [28].

Somatic Complaints

Severity of physical symptoms was measured by means of the Patient Health Questionnaire-15 (PHQ-15) [1]. The PHQ-15

assesses the presence and severity of 15 somatic symptoms (e.g. back pain). A higher score indicates a higher level of somatization. Moreover, scores of 5, 10, and 15 represent cut off points for low, medium, and high somatic symptoms severity, respectively [1].

Psychological Distress

The *depression* and *anxiety* subscales from the validated Brief Symptom Inventory (BSI) were used to assess levels of psychological distress [29]. Individuals rank each symptom on a 5-point Likert scale (from "never" to "very frequently"). Final scores range from 0 to 4 and higher scores represent higher levels of depression and anxiety. Cut-off points of 1.80 and 1.33 are used to define clinical levels of depression and anxiety, respectively [30].

Quality of Life (QoL)

The Short Form Health Survey-12 (SF-12V.2) [31] was used to assess physical and psychological functioning and overall health-related QoL. The SF-12v2 is a well validated measure consisting of 8 domains: general health perception, physical functioning, role limitations due to physical problems, bodily pain, vitality, role limitations due to emotional problems, social functioning and mental health. These 8 dimensions are combined into a physical functioning score (Physical QoL) and a psychological functioning score (Psychological QoL), ranging from 0 to 100, with lower scores representing worst health functioning and QoL.

Physical Activity

Levels were assessed using the Short Questionnaire to Assess Health-Enhancing Physical Activity [32] sports section in which participants indicate the types of physical activities they presently do (e.g. swimming), the frequency per week (e.g. 3 days per week) and duration per day (e.g. 50 minutes). Bicycling and walking frequency were also included. For the purpose of this study, the intensity of each activity was not included. To score the physical activity measure, total minutes of activity is calculated for each activity by multiplying frequency (days/week) and duration (minutes/day). Total physical activity score for each participant was calculated by making the sum of each activity score.

Behavior Regulation Patterns

Using the *All-or-nothing* and *Limiting behavior* scales from The Behavior Responses to Illness Questionnaire (BRIQ) [33]. The first dimension assesses the "boom and bust pattern" usually observed in CFS and the second dimension assesses the limitations in daily activities and the excessive rest that patients take due to their fatigue problems). Higher scores (ranging from 1 to 5) represent a more frequent use of a boom and bust pattern and more reduced daily activities, respectively. Portuguese and Dutch versions of the BRIQ have a very good internal consistency for the All-or-Nothing scale (α =0.84 and α =0.88 (respectively), but much lower although still acceptable alphas for the Limiting behavior scale (0.68 and 0.72, respectively).

Patients' illness representations

Using the Brief Illness Perception Questionnaire (Brief IPQ) [34]. The Brief IPQ consists of 8 items, rated on a 10-point scale, representing 8 illness perceptions: illness consequences, timeline (expected duration of illness), personal control, treatment control, identity (disease label), illness coherence (understanding), illness concern and emotional response. The Brief IPQ dimensions are scored separately. Higher scores on illness consequences, timeline, identity, illness concern and emotional response, indicate a higher perceived impact of CFS. Higher scores on personal control, treatment control and illness coherence, represent more positive illness representations or in other words control over the illness.

Data Analyses

Descriptive data and differences between the Portuguese and Dutch samples for demographics and clinical information related to CFS were explored using univariate chi-square tests (for dichotomous variables) and two-sided t-tests (for continuous variables). Pearson correlation coefficients were conducted to examine the univariate relations between the determinants and the dependent variables (fatigue severity, physical and psychological QoL). For statistical power reasons, only determinants that showed a significant relation with the dependent variables at a $p<.01$ level in either sample were entered in the subsequent hierarchical regression analyses

(Tables 2 and 3). Therefore, the regression analyses examined the respective contribution of the behavioral characteristics (*physical activity, all-or-nothing behavior and limiting behavior*) (block 1) and the illness representations *consequences, personal control, identity, illness concern and emotional response* (block 2) to fatigue severity (Table 4).

In addition, regression analyses were conducted to examine the association between fatigue severity and somatic complaints in on the one hand and Physical and Psychological QoL, on the other hand. There was no multicolinearity between the variables.

For the regression analyses, we considered p values lower than or equal to 0.05 as significant. Data analyses were conducted using the statistical software SPSS v19.

Results

Descriptive and univariate analyses

Table 1 presents descriptive data for both study populations and the results of comparative tests for the following variables: demographic characteristics, working status, use of health care resources, fatigue symptoms, fatigue severity, somatic complaints, psychological distress and QoL (physical and psychological functioning) in Portugal and the Netherlands. A significant difference was found for educational level ($p < 0.05$). Dutch patients had a higher educational level than Portuguese patients. Furthermore, there was a significant difference in working status: 68.7% of the Dutch respondents reported not to be working, while 44.7 % of the Portuguese reported not to work. In addition, there was a longer duration of fatigue symptoms ($p < 0.01$) in the Dutch sample (13.8 ys) than in the Portuguese sample (10.7 y*s*).

No significant differences were found for fatigue severity and subjective experience of fatigue. Both Portuguese and Dutch patients presented high levels of fatigue severity and subjective experience of fatigue. The large majority of the patients in both samples met clinical levels of fatigue. Portuguese patients reported a higher severity of (other) somatic symptoms than Dutch patients ($p < 0.05$). In relation to psychological distress, the Portuguese

CFS patients reported significantly higher levels of depression ($p<$ 0.001) and anxiety ($p<$ 0.001), while significantly more Portuguese participants also reached a clinical level of depression (51.8% vs 10.8%; $p<$ 0.001) and anxiety (64.7% vs 24%; $p<$ 0.001). Both Portuguese and Dutch patients presented low levels of physical and psychological functioning, but the score for psychological functioning was significantly higher in the Dutch population ($p<$ 0.01).

Hierarchical Regression Analyses

Table 4 shows the results of the hierarchical regression models for fatigue severity. In the Portuguese sample, the regression model including the behavioral factors (block 1) was significantly different from the null model ($F(3)=10.022$, $p<0.001$) and explained 27 % of the variance in fatigue severity. Higher levels of physical activity were significantly associated with lower fatigue severity ($p<0.001$). In addition, patients who importantly reduced their daily activities (limiting behavior) presented higher fatigue severity levels ($p<0.05$). Adding illness representations to the model led to an increase of 18% in explained variance (block 2). The belief that chronic fatigue is a very serious problem (identity) and a higher emotional response to CFS were significantly associated with higher fatigue severity levels ($p<0.05$ and $p<0.01$ respectively). The final model explained 45% of the variance in fatigue severity ($F(2)=7.848$, $p<0.001$).

With respect to the fatigue severity in the Dutch sample, the regression model including the behavioral factors (block I) was also significantly different from the null model ($F(2)=11.644$, $p<0.001$) and explained 18% of the variance in fatigue severity. Patients who adopted an all-or-nothing behavior pattern presented higher fatigue severity levels ($p<0.05$). Illness representations (block 2) led to a significant increase in the explained variance (27%). A higher belief in personal control over CFS was significantly associated with lower levels of fatigue severity ($p<0.001$). Furthermore, patients who considered the illness as threatening (consequences) presented higher fatigue severity levels ($p<0.01$). The final model explained 46% of the variance in fatigue severity ($F(8)=16.287$, $p<0.001$).

The regression model for Physical QoL including fatigue severity and somatic complaints was significantly different from the null model, in both the Portuguese ($F(2)=12.262$, $p<0.001$) and the Dutch ($F(2)22.71$, $p<0.001$) sample, explaining respectively 23% and 22% of the variance in this variable. Higher fatigue severity and higher somatic distress were significantly associated with lower levels of physical functioning in Portuguese (ß=-.39, $p<0.001$ and ß=-.23, $p<0.05$, respectively) and Dutch patients (ß =-.17, $p<0.05$ and ß =-.19, $p<0.05$, respectively). Similar results were found for Psychological *QoL*. The regression models including fatigue severity and somatic complaints were significantly different from the null model in both the Portuguese ($F(2)=25.207$, $p<0.001$) and the Dutch sample ($F(2)=12.727$, $p<0.001$), explaining respectively 46% and 14% of the variance in psychological Qol. Higher fatigue severity was significantly associated with lower levels of psychological functioning in both samples (ß =-.49, $p<0.001$ and ß =-.29, $p<0.001$, respectively). In the Portuguese sample, a higher level of somatic distress was also significantly associated with lower psychological QoL (ß =-.34, $p<0.001$).

Discussion

In this cross-cultural study, we found a difference in educational level: the Dutch patients were higher educated. This difference is in line with available data on educational level in these countries [35]. An important finding was the high rate of patients not working at the time of study participation. Even though we do not know why patients were not working, this confirms the high levels of functional impairment in CFS patients [2, 4]. Our results show that this is even much more pronounced in Dutch patients. Apart from cultural differences between both countries, this difference can also be attributed to economical factors and differences in the health care and social security system. Another possible explanation is the significantly longer duration of chronic fatigue that was observed in the Dutch patients.

As expected, in both countries, levels of fatigue severity were very high and the majority of the patients met a clinical level

of CFS. In addition, physical and psychological QoL were poor in both samples, confirming earlier findings showing that high levels of disability are associated with CFS [2, 3]. Fatigue severity and somatic complaints were significantly associated with lower physical QoL in both samples. Psychological functioning was significantly lower and depression and anxiety significantly higher in the Portuguese sample. About half of the Portuguese patients even met clinical levels of anxiety and depression. These results are in line with the cultural differences in the experience and expression of distress between both countries [24]. These important differences in psychological distress can also be explained by the fact that CFS is, in contrast to the Netherlands, not recognized as a specific disorder by primary care health professionals in Portugal. As a result, Portuguese patients may present with higher levels of frustration, anxiety, feelings of loneliness, helplessness and hopelessness [8].

The second study question regards the contribution of behavioral and cognitive variables to fatigue severity in both samples. The regression models explained 45% (Portugal) and 46% (Netherlands) of the variance in fatigue severity. Interestingly, there are important differences in the determinants that were significantly associated with fatigue severity. In relation to the behavioral determinants, higher levels of physical activity were significantly associated with lower levels of fatigue severity in the Portuguese sample, which is in accordance with previous research [36, 37] and strengthens the current recommendation for CFS patients to engage in physical activity rather than refraining from it [38]. Additionally, limiting behavior (reducing daily activities and excessive resting) was also significantly associated with fatigue severity in the Portuguese patients. The fact that Dutch patients were more physically active and that physical activity was not a significant determinant of fatigue severity in this sample backs the importance of tailored physical activity for CFS patients (e.g. Graded Exercise Therapy). However, finding a good balance between activity and rest on a daily basis is equally important [18, 33, 38]. This assumption is reinforced by the fact that a boom-and-bust (all or none behavior) cycle was significantly associated with higher fatigue severity levels in the Dutch patients, which is in line

with previous research [13, 16].

With respect to illness representations, in the Portuguese sample, the belief that CFS is a very serious condition (identity) was significantly associated with higher fatigue severity levels. This result confirms earlier findings that patients who believe that their illness is very severe, adopt more passive ways of dealing with their health problem (such as limiting behavior) and as a result of that, present higher levels of disability and psychological distress [2, 13, 17]. In fact, emotional response was also significantly associated with fatigue severity in the Portuguese sample. Emotional response was a significant determinant only in the Portuguese sample, which is in line with existing differences in psychological distress between the two countries [24]. For Dutch patients, the perception of having personal control over the illness was significantly associated with lower fatigue levels. On the other hand, thinking that CFS has severe consequences was significantly associated with higher fatigue severity. Overall our findings are in line with previous research in which positive illness beliefs are associated with lower fatigue severity and negative beliefs with higher fatigue severity [13].

While these findings are valuable, several limitations of this study should be discussed. A major limitation is that it was carried out in health care centers and patients associations. As a consequence, the results cannot be generalized to the whole CFS population in both countries. In addition, there was a difference in recruitment strategy. Portuguese patients were partly recruited via medical doctors, while all Dutch patients were recruited via e-mail by the patient association only. This may have led to a selection bias. Moreover, due to the fact that the confirmation of the diagnosis of CFS was based on self-reports, it cannot be excluded that some patients do not fulfill all the CDC criteria for CFS. Ideally, this diagnosis should also rule out other somatic and psychiatric causes of the symptoms, by means of a full clinical assessment. Differences between the two samples in depression, anxiety and psychological QoL, can thus also be attributed to differences in diagnosis. Another limitation is the cross-sectional design of the study which limits the conclusions that can be drawn about the causality of the relationships. A longitudinal study would provide

more valid data on the psychological predictors of CFS and the relationship between fatigue severity and disability. Moreover, there were differences in the sample size and only female patients were included in the analyses. Finally, due to the fact that there are no normative data for the Portuguese CIS-20R and the BSI, the comparisons of the respective clinical levels should be interpreted with care.

Despite these limitations, this study is innovative due to fact that cross-cultural research on psychological aspects of CFS is very limited. CFS is considered to be a multi-factorial disorder, with biological, social and psychological factors contributing to its onset and perpetuation. Our findings suggest that fatigue severity and related impairment are very similar in CFS patients from Portugal and The Netherlands, which is in line with the idea that the illness is not restricted to one type of culture [22, 23]. Nevertheless, there seem to be significant differences in psychological distress between the Portuguese and the Dutch patients.

This study shows that a psychological approach can contribute to the understanding and treatment of CFS. The fact that illness representations and behavioral patterns were important determinants of fatigue severity in both countries, suggest that similar interventions, such as psychological interventions that address patients' beliefs about their illness as well as interventions that focus on behavioral regulation or modification strategies should be offered internationally. However, due to the differences found in the specific determinants, interventions should also be tailored to patients' needs and focus more on emotion regulation and the increase of physical activity levels in Portuguese patients, while encouraging personal control and establishing a good balance between daily activities and rest can be important intervention targets for Dutch patients.

Acknowledgements

This study was carried out as part of a grant from the Portuguese Foundation for Science and Technology to the first author (SFRH/BD/47579/2008).

The authors would like to thank the patients that participated in this research, the medical doctors from the Health Care Institutions and the volunteers from the Patients Associations, in both countries.

References

1. Kroenke K., Spitzer, R, Williams JBW. The PHQ-15: Validity of a new measure for evaluating the severity of somatic symptoms. Psychsom Med. 2002;64:258-66.
2. De Gucht V, Maes S. Explaining medically unexplained symptoms: toward a multidimensional theory-based approach to somatisation. J Psychosom Res. 2006;60:349-55.doi: 10.1016/j.jpsychores.2006.01.021.
3. Hardt J, Buchwald D, Wilks D, Sharpe M, Nix WA, Eagle UT. Health-related quality of life in patients with chronic fatigue syndrome: an international study. J Psychosom Res. 2001;51:431-4. doi: 10.1016/S0022-3999(01)00220-3
4. Afari N, Buchwald D. Chronic Fatigue Syndrome: a review. Am J Psych. 2003;160:221-36. doi: 10.1176/appi.ajp.160.2.221
5. Fukuda K, Strauss SE, Hickie I, Sharpe MC, Dobbins, JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Annals Int Med. 1994;121:953-9.
6. Prins JB, Vand der Meer JWM, Bleijenberg G. Chronic fatigue syndrome. The Lancet 2006;367:346-55. doi:.1016/S0140-6736(06)68073-2
7. S.K. Johnson. Depression and fatigue. In: DeLuca J, editor. Fatigue as a window to the brain. Cambridge: MIT Press; 2005. pp. 157-172.
8. Lehman AM, Lehman DR, Hemphill KJ, Mandel DR, Cooper LM. Illness experience, depression and anxiety in chronic fatigue syndrome. J Psychosom Res. 2002;56:461-5. doi:10.1016/S0022-3999(02)00318-5
9. Harvey SB, Wadsworth M, Wessely S, Hotopf M. The relationship between prior psychiatric disorder and chronic fatigue: evidence from a national birth cohort study. Psychol Med. 2008;38:933-40.doi: 10.1017/S0033291707001900
10. Clark C, Goodwin L, Satnsfeld SA, Hotopf M, White PD. Premorbid risk markers for chronic fatigue syndrome in the 1958 British birth cohort. Brit J Psych. 2011;199:323-9. doi: 10.1192/bjp.bp.110.083956
11. Allen LA, Escobar JL. Fatigue and somatization. In: DeLuca J, editor. Fatigue as a window to the brain. Cambridge: MIT Press; 2005. pp. 173-183.
12. Knottnerus JA. Advisory report on chronic fatigue syndrome. Health Council of the Netherlands. 2005. http://www.gezondheidsraad.nl/sites/default/files/05@02E.pdf. Accessed 12 Jan 2012.

13. Moss-Morris R. Symptom perceptions, illness beliefs and coping in chronic fatigue syndrome. J Ment Health 2005; 14:223-35. doi: 10.1080/09638230500136548
14. Leventhal H, Leventhal EA, Contrada R J. Self regulation, health, and behavior: a perceptual-cognitive approach. Psychology & Health 1998; 13:717-33. doi: 10.1080/08870449808407425
15. Weinman J, Petrie KJ, Moss-Morris R, Home R. The illness perception questionnaire: a new method for assessing illness perceptions. Psychology & Health 1996; 11:431-46. doi:10.1080/08870449608400270
16. Moss-Morris R, Spence MJ, Hou R. The pathway from glandular fever to chronic fatigue syndrome: can the cognitive behavioral model provide the map? Psychol Med. 2011;41:1099-107. doi:10.1017/S003329171000139X.
17. Heijmans MJWM. Coping and adaptive outcome in chronic fatigue syndrome: importance of illness cognitions. J Psychosom Res. 1998;45:39-51.
18. Graded Exercise Therapy: A self-help guide for those with chronic fatigue syndrome/myalgic encephalomyelitis. NHS Foundation Trust and St. Bartholomew's Hospital 2009. http://drleigh.org/wp-content/uploads/2008/12/chronic-fatigue-exercise-program-specifics.pdf. Accessed 20 May 2009.
19. Fulcher KY, White PD. Strength and physiological response to exercise in patients with chronic fatigue syndrome. J Neurol Neurosurg Psych. 2000;69:302-7. doi:10.1136/jnnp.69.3.302
20. Price JR, Mitchell E, Tidy E, Hunot V.Cognitive behaviour therapy for chronic fatigue syndrome in adults. Cochrane Database Syst Rev. 2008;3:CD001027.
21. McGuire L, Edmonds L, Price JR. Exercise therapy for chronic fatigue syndrome. Cochrane Database Syst Rev. 2004;3:CD003200.
22. Hickie I, Davenport T, Vernon SD, Nisenbaum R, Reeves WC, Hadzi-Pavlovic D, Lloyd A. Are chronic fatigue and chronic fatigue syndrome valid clinical entities across countries and health-care settings? Aust N Z J Psych. 2009;43:25-35. doi:10.1080/00048670802534432
23. Jo Cho H, Menezes PR, Hotopf M, Bhugra D, Wessley S. Comparative epidemiology of chronic fatigue syndrome in Brazilian and British primary care: prevalence and recognition. Brit J Psych. 2009; 194:117-22. doi:10.1192/bjp.bp.108.051813
24. Eurobarometer. Mental Health. Special eurobarometer 345/Wave

73.2. European Comission; 2010.
25. Eurobarometer. Health and food. Special eurobarometer 334/Wavw 72.3. European Comission; 2010.
26. Vercoulen JHMM, Alberets M, Bleijenberg G: De Checklist Individual Strenght (CIS). Gedragstherapie 1999;32:31-6.
27. De Vree B, Van der Werf S, Prins J, Bazlmans E, Vercoulen J, Servaes P. Meetinstrumenten bij chronische vermoeidheid. Gedragstherapie 2002;35:157-64.
28. Marques M, De Gucht V, Maes S, Leal I. Relação entre exercício físico e fadiga percebida. In: Maia A, Silva S, Pires T, editors. Proceedings of the I congress on health and behaviour of the Portuguese speaking countries. Braga: CIPSI Edições; 2009. pp.505-511.
29. Degoratis L. Brief Symptom Inventory: administration, Scoring and Procedures Manual. 3rd ed. Minneapolis: National Computer System;1993.
30. De Beurs E, Zitman F The Brief Symptom Inventory (BSI): de betrouwbaarheid en validiteit van een handzaam alternatief voor de SCL-90. Maandblad Geestelijke Volksgezondheid 2005;61:120-141.
31. Ware JE, Kosinski M, Turner-Bowker DM, Gandek B. How to score version 2 of the SF-12® Health Survey. Lincoln, RI: Quality Metric Incorporated; 2002.
32. Wendel-Vos GCW, Schuit AJ, Saris, WHM, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epid. 2003;56:1163-69. doi: 10.1016/S0895-4356(03)00220-8
33. Spence M, Moss-Morris R, Chalder T. The behaviour responses to illness questionnaire (BRIQ): a new predictive measure of medically unexplained symptoms following acute infection. Psychol Med. 2005;35:583-93. doi:10.1017/S0033291704003484
34. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J Psychosom Res. 2006; 60:631-7. doi:10.1016/j.jpsychores.2005.10.020
35. Key data on Education in Europe. European Comission; 2009. Brussels: Education, Audiovisual and Culture Executive Agency.
36. Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome BMJ 1997;314:1647-52. doi:10.1136/bmj.314.7095.1647
37. Moss-Morris R, Sharon C, Tobin R, Baldi JC. A randomised

controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. J Health Psychol 2005;10:245-59. doi:10.1177/1359105305049774
38. National Institute for Health and Clinical Excellence. Guideline 53: chronic fatigue syndrome/ myalgic encephalomyelitis (or encephalopathy). London; 2007.

Table 1 Descriptives and differences in demographics and clinical characteristics, fatigue severity, somatic complaints, psychological distress and QoL for the Portuguese and the Dutch CFS samples

	Portugal (N=85)	**Netherlands** (N=167)	**Test for diferences**
Female patients, no. (%)	100	100	
Age, years	47.54 ± 10.75	44.93 ± 10.98	*t=1.77*
Educational level, no. (%)			X^2=7.02*
Primary and Lower education	27.4	16.2	
Secondary education	39.3	34.7	
Tertiary education	33.3	49.1	
Not working, no. (%)	44.7	68.7	X^2=13.5**
Illness duration, months	128.81±102.41	165.71 ± 92.22	*t*= -2.85**
Medical visits, no.	4.64±3.42	4.28±4.67	*t*=0.59
CDC CFS Diagnosis, no. (%)	100	100	-
Fatigue severity	101.75 ± 17.60	99.52 ± 16.61	*t*=0.99
Subjective experience of fatigue	46.73 ± 6.88	46.34 ± 7.96	*t*=0.38
Subjective experience, no. (%)			X^2=0.47
Non clinical	7.1	9.6	
Clinical	92.9	90.4	
Somatic complaints	15.53 ± 4.11	14.29 ± 4.24	*t*=2.20*
Somatic complaints, no.(%)			X^2=3.51
Low	7.1	13.5	
Medium	42.4	46.0	
High	50.6	40.5	
Depression	1.72 ± 0.92	0.84 ± 0.78	*t*=7.61**
Depression, no. (%)			X^2=53.09**
Non clinical	48.2	89.8	
Clinical	51.8	10.2	
Anxiety	1.67 ± 0.79	0.79 ± 0.77	*t*=8.42**
Anxiety , no. (%)			X^2=39.83**
Non clinical	35.3	76.0	
Clinical	64.7	24.0	
Physical QoL	37.22 ± 18.40	34.83 ± 16.91	*t*=1.03
Psychological QoL	39.31 ± 16.97	45.26 ± 9.22	*t*=-3.61**

**p <0 .05. **p<0.01. Values are the mean ± SD unless otherwise indicated.*

Table 2 Correlations (Pearson) for age, illness duration, fatigue severity, somatic complaints, QoL, psychological distress, behavioral and cognitive factors in the Portuguese sample

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Age	1																
Illness duration	0.20	1															
Fatigue severity	-0.14	0.12	1														
Somatic complaints	-0.16	0.07	0.32*	1													
Physical QoL	-0.03	-0.17	-0.43*	-0.35*	1												
Psychological QoL	0.07	0.00	-0.60*	-0.50*	0.51*	1											
Physical activity	0.02	0.04	-0.31*	-0.02	0.02	0.15*	1										
All-or-nothing	-0.03	0.11	0.31*	-0.26	-0.26	-0.27	-0.12	1									
Limiting behavior	-0.26*	0.17	0.38*	-0.31*	-0.31*	-0.40*	-0.06	0.18	1								
Consequences	-0.15	0.10	0.37*	-0.54*	-0.54*	-0.44*	-0.01	0.28*	0.35*	1							
Timeline	-0.10	0.09	-0.01	0.17	0.17	-0.11	0.08	0.17	-0.01	0.29*	1						
Personal control	0.12	-0.05	-0.25	0.31*	0.31*	0.16	0.12	-0.14	-0.13*	-0.25*	-0.06	1					
Treatment control	0.11	-0.04	-0.26	0.09	0.09	0.12	0.03	-0.23	-0.10	-0.12	-0.04	0.28*	1				
Identity	-0.14	0.13	0.37*	-0.47*	-0.47*	-0.27	0.16	0.25	0.31*	0.44*	0.09	-0.12	-0.07	1			
Concern	-0.12	-0.02	0.18	-0.44*	-0.44*	-0.27	0.03	0.18	0.18	0.46*	0.21	-0.17	0.02	0.28	1		
Comprehensibility	-0.08	0.06	-0.12	-0.02	-0.02	0.05	0.10	-0.01	-0.21*	-0.07	0.00	0.19	0.27	0.03	-0.01*	1	
Emotional response	-0.01	0.13	0.43*	-0.38*	-0.38*	-0.51*	0.03	0.16	-0.24*	0.60*	0.29*	-0.22	-0.14	0.23	0.57*	-0.11	1
M	47.54	128.81	101.75	15.53	37.22	39.31	64.76	3.11	3.11	7.74	8.19	4.49	4.89	6.80	7.66	5.76	8.04
SD	10-75	102.41	17.60	4.11	18.40	16.97	109.76	0.81	0.67	2.14	2.40	2.86	2.60	2.23	0.254	3.18	2.20

*$p < .01$

Table 3 Correlations (Pearson) for age, illness duration, fatigue severity, somatic complaints, QoL, psychological distress, behavioral and cognitive factors in the Dutch sample

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Age	1																
Illness duration	0.35*	1															
Fatigue severity	-0.18	-0.15	1														
Somatic complaints	0.03	0.03	0.36*	1													
Physical QoL	0.05	0.01	-0.43*	-0.30*	1												
Psychological QoL	-0.01	0.06	-0.34*	-0.25*	-0.44*	1											
Physical activity	0.02	-0.00	0.00	-0.07	-0.02	-0.02	1										
All-or-nothing	-0.06	-0.02	0.20*	0.23*	-0.18	-0.30*	-0.03	1									
Limiting behavior	0.04	-0.29*	0.33*	0.08	-0.40*	-0.26*	-0.08	-0.16	1								
Consequences	-0.11	-0.01	0.48*	0.20*	-0.56*	-0.21*	-0.04	0.01	0.37*	1							
Timeline	0.26*	0.32*	-0.02	0.19	-0.08	0.14	-0.02	-0.06	-0.09	0.16	1						
Personal control	0.08	0.21*	0.53*	-0.19	0.28*	0.21*	-0.02	-0.05	-0.29*	-0.36*	0.07	1					
Treatment control	-0.07	-0.03	-0.15	-0.16	0.01	0.00	-0.05	-0.01	-0.07	-0.03	-0.19	0.16	1				
Identity	-0.04	0.06	0.46*	0.40*	-0.29*	-0.29*	-0.07	0.10	0.31*	0.68*	0.28*	-0.38*	-0.19	1			
Concern	-0.03	-0.17	-0.37*	0.30*	-0.25*	-0.25*	-0.04	0.12	0.29	0.34*	0.16	-0.33*	-0.04	0.48*	1		
Comprehensibility	-0.10	0.14	0.11	-0.12	0.06	0.06	-0.01	-0.11	-0.04	-0.05	-0.05	0.26*	0.05	-0.07	-0.23*	1	
Emotional response	-0.13	-0.13	0.38	0.32*	-0.24*	-0.24*	-0.06	0.16	0.24*	0.27*	0.16	-0.27*	-0.07	0.38*	0.48*	-0.16	1
M	44.93	162.71	99.52	14.29	34.83	45.26	201.89	2.42	3.31	8.82	8.12	4.93	4.56	8.00	5.90	6.30	6.00
SD	10.98	92.22	16.61	4.24	16.91	9.22	210.419	0.65	0.62	1.40	1.87	2.12	2.36	1.46	2.45	2.39	2.38

*$p < .01$

Table 4 Hierarchical regression analyses for fatigue severity by country

	Fatigue Severity			
	Portugal		**Netherlands**	
Predictors	ΔR^2	ß	ΔR^2	ß
Block 1 (behavioral factors)	0.27**		.018**	
Physical activity		-0.31**		0.03
All-or-nothing behavior		0.13		0.16*
Limiting behavior		0.20*		0.12
Block 4 (Illness representations)	0.18**		0.27**	
Consequences		-0.03		0.22**
Personal Control		-0.09		-0.34**
Identity		0.25*		0.08
Concern		-0.16		0.03
Emotional response		0.38**		0.14
R^2	0.45		0.46	
Adj. R^2 Model	0.40**		0.43**	

Note. Standardized beta coefficients (ß) represent the beta at final entry.
p<.05,p<.01*

04

Differential effects of behavioral interventions with a graded physical activity component in patients suffering from Chronic Fatigue (Syndrome): An updated systematic review and meta-analysis

Manuscript under revision
M. Marques, V. De Gucht, M.J. Gouveia, I. Leal & S. Maes (XXXX). Differential effects of behavioral interventions with a graded physical activity component in patients suffering from Chronic Fatigue (Syndrome): An updated systematic review and meta-analysis.

Abstract

An updated systematic review and meta-analysis was conducted to (1) evaluate the effects of behavioral and psychological interventions containing a graded physical activity component upon fatigue severity, physical functioning, physical activity and psychological distress, and to (2) examine potential moderator effects of trial characteristics (type of control, setting, provider, length of treatment, psychological component, flexibility in physical activity, and minimal face to face patient-provider contact). Pertinent content of selected studies was extracted and rated on a scale of methodological quality. Sixteen randomized controlled trials (N= 1843) were included in the meta-analyses. Significant small to medium effect sizes (Hedge's *g*) were found for all outcomes at post-treatment and follow-up (*g*=0.22 to *g*=0.67), with the exception of physical activity at post-treatment (*g*=0.11). The largest effects were found for fatigue severity (*g*=0.62 to *g*=0.67). Subgroup analyses revealed that minimal contact interventions had additional beneficial effects upon fatigue and depression. Interventions provided by psychologists-psychotherapists and interventions conducted in secondary-tertiary settings also resulted in more beneficial effects on fatigue. We found some indication of publication bias. The small number of studies and variability between them are limitations of this study. Future research should explore additional moderating effects in order to improve the effectiveness of interventions.

Keywords: Meta-analysis, chronic fatigue, graded physical activity/exercise, moderators, psychological, interventions.

Highlights

Interventions including physical activity have beneficial effects on chronic fatigue.

The number of trials is modest and there is heterogeneity between them.

Type of setting and provider of treatment moderate fatigue severity effect sizes.

Minimal direct contact interventions are promising.

Introduction

Chronic Fatigue (or Idiopathic Chronic Fatigue-ICF) is a condition characterized by the presence of new onset unexplained persistent fatigue (lasting for at least 6 months) that is not alleviated by rest, is debilitating and leads to significant functional impairment. Commonly, these patients experience additional rheumatologic and neuropsychiatric symptoms (Lehman, Lehman, Hemphill, Mandel, & Cooper, 2002; Afari & Buchwald, 2003;). When at least four of these symptoms are present (i.e. unrefreshing sleep, lengthy malaise after exertion lasting for over 24 hours, impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain without swelling or redness and headaches of a new type or severity) it is diagnosed as Chronic Fatigue Syndrome (CFS; or Myalgic Encephalomyelitis-ME) according to the widely used Centres for Disease Control and Prevention (CDC) criteria (Fukuda et al., 1994). Another set of diagnostic criteria commonly used is the Oxford Criteria (Sharpe, 1991), which differs from the CDC criteria in that the Oxford Criteria requires mental fatigue to be present, but do not require the presence of additional somatic symptoms. A panel of experts has recently proposed a new international consensus criterion (Carruthers et al., 2011), which does not require the presence of fatigue for at least 6 months, but requires the presence of post-exertional malaise as well as the presence of at least three symptoms related to neurological impairments (e.g. headaches), three immune, gastro-intestinal and/or genito-urinary symptoms (e.g. nausea), and one symptom related to energy production/transport impairments (e.g. subnormal body temperature).

The prevalence of CFS/ME is reported to be in between 0.007% and 2.6% in general population samples, varying according to several factors such as the criteria used to diagnose CFS/ME (Ranjith, 2005). It is more common in younger adults and among women (Afari & Buchwald, 2003). In terms of prognosis, full recovery rates are low, but it is common for patients to experience an improvement in symptom severity (Cairns & Hotpof, 2005). CFS/ME is also associated with a high use of health care resources and represents an important

socioeconomic burden (Sabes-Figuera et al., 2010).

Physical activity and Chronic Fatigue

Several studies emphasize the fact that lack of physical activity and prolonged physical inactivity (rest) can result in physical deconditioning as well as in other physiological and psychosocial consequences that may perpetuate fatigue and physical disability (Fulcher & White, 2000; Clark, Clark, & White, 2005; Nijs, Wallman, & Paul, 2011b). It has therefore been recommended that CFS/ME patients engage in physical activity/exercise instead of refraining from it (NICE, 2007). Physical activity that is too vigorous can however perpetuate fatigue symptoms (Nijs, Paul, & Wallman, 2008; Nijs et al., 2011b). Patients' perceptions and expectations with respect to symptom exacerbation as a consequence of physical exertion can lead to fear of physical activity (Clark et al., 2005; Prins, Van der Meer, & Bleijenberg, 2006; Nijs et al., 2008) and explain the reduced levels of physical activity found in patients with chronic fatigue (Van der Werf, Prins, Vercoulen, van der Meer, & Bleijenberg, 2000; Nijs, et al., 2011a). Not surprisingly, it is common to find a "boom-and-bust pattern" (or "all-or-nothing" behavior) in these patients, which is the systematic alternation between periods of over-activity (when feeling good) and, as a consequence of that, feeling extremely fatigued and having to rest for longer periods of time. For these reasons, physical activity should be balanced, gradually introduced and offered with caution to CFS/ME patients (Clark et al., 2005; NICE, 2007; Nijs et al., 2011b).

Graded Exercise Therapy (GET) has been recommended as a treatment for CFS/ME patients (NICE, 2007). GET is based on the assumption that aerobic exercise (e.g. brisk walking) or physical activity (e.g. housework, gardening) must be initiated at a level (intensity and frequency) that doesn't exacerbate symptoms and must be gradually increased until patients reach an optimal level of activity. GET follows the exercise prescription guidelines from the American College of Sports Medicine, tailored to each patient's initial level of physical capacity. Most GET interventions follow a similar protocol (Fulcher & White, 1998). GET is usually delivered by an exercise physiologist or physical therapist, and

consists of supervised aerobic exercise sessions and/or home-based aerobic exercise prescription (e.g. walking). GET focuses on avoiding overexertion by advising patients not to exceed the recommended levels of physical activity/exercise. At the same time, in most GET interventions patients are encouraged not to reduce or stop doing physical activity/exercise when symptoms get worse. Recent approaches to GET have advocated that flexibility in graded exercise programs according to individual tolerance levels can be beneficial for CFS/ME patients. This implies that exercise can be reduced or even stopped when symptoms get worse (Nijs et al., 2008; Wallman, Morton, Goodman, Grove, & Guilfoyle, 2004). A Cochrane review (Edmonds, McGuire, & Price, 2004) and a recent meta-analysis (Castell, Kazantsis & Moss-Morris, 2011) reported beneficial effects of GET on fatigue severity and functional impairment in patients with chronic fatigue.

Because of the benefits of physical activity for patients suffering from CFS/ME, a large number of Cognitive Behavioural Therapy (CBT) trials have incorporated a graded physical activity/exercise component. The primary focus of CBT for these patients is on challenging cognitions and behaviors related to the perpetuation of fatigue (e.g. somatic illness attributions). Patients are encouraged to engage in a gradual increase of physical activity and to balance daily activities (e.g. activity and rest). In addition, sleep hygiene is usually addressed and patients are supported to set goals for functional recovery. The positive effects of CBT upon chronic fatigue management have been shown in a Cochrane review (Price, Mitchell, Tidy, & Hunot, 2008) and in two meta-analyses (Malouff, Thorsteinsson, Rooke, Bhullar, & Schutte, 2008; Castell et al., 2011). Some CBT approaches distinguish between relative-active patients (characterized by an alternation of over-activity and rest) and low-active patients and intervene accordingly (Bleijenberg, Prins, & Bazelmans, 2003).

Another recent approach to CFS is multidisciplinary rehabilitation, consisting of a combination of treatments such as CBT, a gradual increase in physical activity/exercise, balancing daily physical activities and rest according to the patients' symptoms, increasing awareness of the body and its relation to psychological well-being, and social/functional reintegration, tailored to patients'

needs and goals (Cox, 1999; Thomas, Sadlier, & Smith, 2008; Vos-Vromans et al., 2012). As there is a lack of evaluation studies of this approach, it is difficult to draw conclusions with respect to its effects.

Previous meta-analyses

Two meta-analyses tried to compare the efficacy of physical activity interventions to psychological interventions in patients with chronic fatigue. The first one, conducted by Malouff and colleagues in 2008 reviewed the effects of CBT, including 12 trials (1371 patients). Overall, there was a medium effect size (d=0.48) for fatigue. A comparison of interventions containing only a (graded) activity component to interventions containing, next to activity, a cognitive component, did not yield significant differential effects (d=0.60 and d=0.43, respectively). Other moderator analyses (treatment format, type of comparison group, sample type, diagnostic criteria used, number of hours of treatment, number of sessions, and number of months of follow-up) also did not result in significant differential effects.

The meta-analysis by Castell and colleagues (2011) compared the effects of GET (n=5) vs. CBT (n=16) trials upon the following outcomes: fatigue severity, functional impairment, and psychological distress (anxiety and depression). Both types of intervention presented similar overall post-treatment effects (g=0.28 and g=0.33, respectively) for CFS patients. The overall effect sizes for anxiety and depression were however higher within the CBT subset. In addition, the authors also examined potential moderator effects of study characteristics that were previously analysed in the Malouff et al. (2008) meta-analysis (type of comparison group, treatment format, number of hours of treatment, and diagnostic criteria used) as well as treatment setting, and treatment duration. Number of treatment hours was a significant predictor of treatment effects, but accounted only for a small proportion of the variance of the effects (Castell et al., 2011).

Both meta-analyses (Malouff et al., 2008; Castell et al., 2011) have however limitations worth mentioning. First, in the Malouff et al (2008) study the authors aimed to evaluate the effects of CBT interventions, but also considered trials with an emphasis on GET

as a type of CBT as they included them in the overall effect. Second, in the comparison between "activity treatments" and "activity plus cognitive treatments", the authors included studies in the "activity treatments" category that had a cognitive component (e.g. Powell, Bentall, Nye, & Edwards, 2001). In the meta-analysis conducted by Castell and colleagues (2011), this same trial was included in the group of CBT trials. Third, in the Castell et al. meta-analysis (2011), potential moderators were analyzed only for the group of CBT trials, due to a low heterogeneity found in the GET group. In addition, several of the CBT trials included graded exercise components, limiting the conclusions that can be drawn from a comparison between CBT and GET interventions. Finally, Malouff and colleagues (2008) did not distinguish between post-treatment and follow-up results and only post-treatment effects were presented in the Castell et al study (2011).

Focus of the systematic review and meta-analysis

In this study, we intend to address some of these limitations and extend the scope of the meta-analysis in the following ways. First, no meta-analysis has yet assessed the effects of behavioural and psychological interventions on physical activity among CFS/ME patients, which is a key behaviour targeted in interventions for chronic fatigue management. Second, there are a number of recently published trials assessing the effects of GET, CBT with a graded exercise component, and rehabilitation approaches that were not included in the previous reviews and meta-analyses. Third, several interventions targeting CFS/ME patients present specific treatment characteristics that have not yet been taken into account as moderators: (1) flexibility in physical activity/exercise levels and goals, in accordance with patients' exercise tolerance (Nijs et al., 2011b); and (2) minimal contact interventions as compared to more intensive interventions.

Based on recent systematic reviews on minimal contact and self-help treatments (Cuijpers, Donker, van Straten, Li & Anderson, 2010; Haug, Nordgreen, Ost, & Havik, 2012; Ahl, Mikocka-Walus , Gordon &Andrews, 2013; Pajak, Lackner, & Kamboj, 2013), we considered minimal-contact interventions as self-management interventions that consisted of a maximum of three initial face-to-

face sessions followed by remote additional guidance and feedback during the treatment period (e.g. by email, telephone). Usually these interventions also provide patient manuals with information and assignments related to disease management. Most CBT and GET interventions are typically resource-intensive, as they usually require considerable direct provider-patient contact. Recent reviews have revealed that minimal contact interventions are promising for the treatment of various psychological (e.g. Haug et al, 2012) and physical symptoms (e.g. Pajak et al., 2013). In addition, recent controlled trials of minimal contact interventions in CFS/ME showed promising results (e.g. Tummers, Knoop, van Dam, & Bleijenberg, 2012).

The aims of the current systematic review and meta-analysis are thus:

1- To determine the overall effect of behavioral interventions with a graded physical activity/exercise component on fatigue severity, physical functioning/functional impairment, physical activity and physical capacity, as well as psychological distress (anxiety and depression); both at post-treatment and at follow-up, among patients with ICF and CFS/ME.

2- To examine whether the effects on these outcomes are moderated by the type of care provided to the control condition, the treatment setting, the treatment provider, and the length of treatment.

3- To examine if treatment effects are influenced by the presence of a psychological component in the treatment, by flexibility in physical activity levels or goals, and by the amount of contact between provider and patient (intensive versus minimal contact).

Methods

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (Liberati et al., 2009) statement and APA's Meta-Analysis Reporting Methods (APA, 2008).

Eligibility criteria

Types of participants

Studies were included if they were conducted in adult patients presenting (Idiopathic) Chronic Fatigue or Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME).

Types of interventions

Studies had to include an arm of a behavioral and/or psychological intervention with a graded physical activity/exercise component, targeting chronic fatigue management.

Types of comparisons

Studies had to include a control condition, consisting of usual care, waiting list control, or another type of intervention (e.g. relaxation).

Types of outcomes

Studies had to present statistical data allowing the calculation of effect sizes, on at least one of the following outcomes - fatigue severity, functional impairment/physical functioning, physical activity and/or physical capacity, and psychological distress (depression and/or anxiety), measured at baseline (pre-treatment), at post-treatment and/or at follow-up.

Types of studies

Studies were included if they were randomized controlled trials (RCTs) published in peer review journals in English.
There were no restrictions with respect to the type of diagnostic criteria used, setting, format and source of delivery of the intervention, as well as with respect to the length of the intervention and follow-up measurement point(s).

Search strategy and study selection

Initially, electronic databases (MEDLINE, Cochrane Database of Clinical Trials, PsychINFO and Web of Science) were searched for relevant articles published between 1988 and 2013 to coincide with the first diagnosis criteria for CFS (Holmes et al., 1988). A comprehensive search strategy was used, with the combination of

the following keywords: chronic fatigue or unexplained chronic fatigue or idiopathic chronic fatigue or chronic fatigue syndrome or CFS or myalgic encephalomyelitis or ME, psychological or cognitive or behavior(u)r or CBT or graded exercise therapy or exercise or physical activity or aerobic or rehabilitation, and treatment or intervention or trial or RCT (complete search strategies can be obtained from the authors). Next, content pages of key journals were browsed (e.g. *Journal of Psychosomatic Research*). Finally, reference lists from previous review articles and included studies were hand searched to find additional studies (Appendix A).

One author (MM) and an independent researcher (AC) read the titles and abstracts retrieved. If the studies appeared to meet the inclusion criteria, full texts were obtained and reviewed by the first author (MM). A second author (SM) checked and approved the final selection of studies.

Coding of study characteristics

Two researchers (MM and MJG) independently coded characteristics from selected studies using a pre-specified form developed by the authors (Complete coding form is available from the authors). The following information was extracted from each selected study: 1) bibliographic information (authors, year of publication, country and reference); 2) type of diagnostic criteria (CDC, Oxford, other); 3) sample characteristics (sample size, gender, age); 4) setting (primary care, secondary-tertiary, university setting); 5) provider (psychologist/psychotherapist, exercise physiologist, physical therapist, nurse, occupational therapist, other); 6) type of care provided to the intervention group (graded physical activity/exercise therapy, cognitive-behavioral treatment, rehabilitation treatment, other behavioral and psychological approaches); 7) type of care provided to the control group (passive control – waiting list control, treatment as usual, other; active control– relaxation/flexibility, counseling, other); 8) format of delivery (individual or group; face-to-face, telephone, email); 9) length of intervention and number of patient-provider sessions, 10) drop-out rate, 11) outcomes assessed (fatigue severity, physical functioning/impairment, physical activity, physical

capacity, depression, anxiety, other) ; 12) measures used to assess outcomes (type and name of measure); and 13) assessment periods (baseline, post-treatment and follow-up).

In addition, the following characteristics were coded: 1) presence vs. absence of a psychological component within the intervention (e.g. cognitive behavioral therapy); 2) presence vs. absence of flexibility in setting physical activity/exercise levels or goals; 3) whether the intervention was a minimal or a more intensive intervention in terms of direct (face to face) contact hours. These characteristics were coded as 1 (yes) and 0 (no). (Complete coding form can be obtained from the authors).

The average inter-rater agreement was very good (Cohen's kappa= 0.84). Disagreements in coding were resolved by consensus between the two coders (MM and MJG). A third researcher (SM, VDG) resolved any remaining disagreements.

Quality and risk of bias assessment

The methodological quality of the included trials was assessed using a 29-item modified version of the Cochrane Collaboration Depression, Anxiety and Neurosis Review Group (CCDAN) quality rating scale (Lackner, Mesmer, Morley, Dowzer, & Hamilton, 2004; Moncrieff, Churchill, Drummond, & McGuire, 2001), validated by Lackner and colleagues (Lackner et al., 2004). The scale assesses characteristics of both internal and external validity of trials. Each item is scored 0 (not done and/or not reported), 1 (done and/or reported to some extent) or 2 (adequately done and/or adequately reported), with the exception of items 23 (Interests declared) and 29 (Consecutive subjects), which are scored 0 or 2. Total scores range from 0 to 58; higher scores indicate higher methodological quality. Risk of bias (high/low/uncertain) was classified based on the following items from this scale: Selection bias - concealment of allocation (item 6); Detection bias - blinding of assessors (item 13); Attrition bias (incomplete outcome data) - Information on attrition (item 16) and inclusion of drop-outs in analyses (item 19), following the guidelines contained in the Cochrane collaboration's tool for assessing risk of bias (Higgins et al., 2011).

Discrepancies in quality rating were resolved by consensus between the two coders (MM and MJG). Inter-rater agreement was satisfactory (Cohen's kappa= 0.68).

Data extraction

Effect sizes (ES) were the standardized mean difference [(mean a-mean b/ pooled change SD)] with Hedge's *g* correction for small samples (Hedges, 1981). To calculate effect sizes for selected outcomes, we extracted sample sizes and baseline, post-treatment and/or follow-up means and standard deviations (SD) for the intervention and control groups. Authors of included studies were contacted when necessary to retrieve missing data in published reports. If this information remained unavailable, the following alternative information was extracted to calculate the effect sizes: 1) post-treatment and/or follow-up means, SD and sample size for each group; 2) Mean difference, 95% confidence interval and samples size for independent group comparisons 3) sample size and p value for independent group comparison, and 4) raw difference in means and confidence limits for independent groups. When reported in the original trials, we used data from intention-to-treat analyses. If there was more than one follow-up assessment point available, the longest period available without crossovers was chosen. This was the case for four trials (Deale, Chalder, Marks, & Wessely, 1997; Fulcher & White, 1997; Powell et al., 2001, Sharpe et al. 1996). In one study the pooled (post-treatment and follow-up) mean and SD was used for the effects of the intervention on physical activity at follow-up, as this was the only statistical information available (O'Dowd, Gladwell, Rogers, Hollinghurst, & Gregory, 2006). When several measures were reported for the same outcome (e.g. physical functioning/ impairment), we chose the measure most commonly used across the studies included.

In the case of studies presenting more than one intervention group meeting eligibility criteria, the following choices were made regarding the selection of the intervention group for inclusion in the meta-analysis: 1) for the trial conducted by White and colleagues (2011) the *Graded Exercise Therapy* intervention arm was selected, since the other intervention arms (Adaptive Pacing and Cognitive-behavioral Therapy) were not exercise oriented

interventions; 2) in the case of the trial conducted by Jason et al. (2007) the *Cognitive-Behavioral Therapy* intervention arm with a graded aerobic physical activity component was selected; 3) for the study conducted by Powell and colleagues (2001), for which there were three intervention arms differing in treatment-dose (Minimum intervention, Telephone intervention and Maximum intervention), the *Minimum Intervention* arm was chosen as there were no significant differences in the effect sizes between the three intervention arms. Regarding control comparisons, in the case of the trial conducted by Jason and colleagues (2007), the *Active Relaxation* condition was chosen as the control comparison due to its similarities with other control conditions included in this meta-analysis.

Data Analyses

Analyses were conducted using the Comprehensive Meta-Analysis Software version 2.2 (Borenstein, Hedges, Higgins, & Rothstein, 2005). We conducted separate meta-analyses for each outcome (fatigue severity, functional impairment/physical functioning, physical activity and physical capacity, depression and anxiety) and for each measurement point (post-treatment and follow-up).

Meta-analyses were conducted using the recommended random-effects model, in which the summary effect is an estimate of the mean of a distribution of effect sizes (Borenstein, Hedges, Higgins, & Rothstein, 2009); the only exceptions were the analyses for the effects of the interventions upon physical activity and physical capacity at post-treatment and follow-up, in which the fixed-effect model was used, due to the limited number of studies (<5 studies) available for the analysis (Borenstein et al., 2009). Effect sizes (ES) were the standardized mean difference with Hedge's *g* correction (Hedges, 1981), interpreted according to Cohen's (Cohen, 1992) guidelines (values of 0.20, 0.50 and 0.80 correspond to small, medium and large effect sizes). Z-values and corresponding p-values were considered as indicator of the significance of the effect. We also inspected the standard residuals (i.e. how much each study differs from the overall effect) for outliers (>1.96).

Meta-analyses were inspected for heterogeneity using: 1) Cochran's *Q* statistic (Cochran, 1954), for which a significant

p-value (<.05) demonstrates that studies don't share a common effect size (i.e. there is heterogeneity in the effect sizes between studies); and 2) I^2 statistic (Julian, Simon, Jonathan, & Douglas, 2003) that assesses the proportion of observed dispersion that is real (i.e. that is due to real differences in the true effect sizes). The I^2 ranges from 0 to 100%, with values of 25%, 50% and 75% reflecting low, moderate and high heterogeneity (Julian et al., 2003).

Whenever heterogeneity of effect sizes was observed (Q p<.05 or I^2 ≥50%), subgroup analyses were conducted to examine whether effect sizes varied according to the following potential moderators: type of control group (coded as passive or active); setting (coded as primary care, secondary-tertiary care, university setting); provider of the treatment (coded as psychologist, psychiatrist or psychotherapist, exercise physiologist or physical therapist, and nurse); psychological intervention component (coded as yes or no); flexibility in physical activity program (coded as yes or no); and minimal contact (coded as yes or no). Subgroup analyses were conducted using mixed-effect models (i.e. random-effects model is conducted within subgroups and a fixed-effect model was used across subgroups; Borenstein et al., 2009). Between-groups Q statistic and corresponding p-values was used to compare the mean effect across subgroups, when there were at least three studies in each subgroup. Due to statistical power effects on the significance of p-values, we also considered within-groups estimate points (Hedge's g), confidence intervals (CI), and the I^2 statistic (Borenstein et al., 2009). Further, meta-regression analyses using random-effect models were conducted to analyze the moderation effect of the continuous variable length of treatment (in weeks) on treatment effect. Meta-regressions were analyzed based on the Z-value and associated p-value of the slope and were only conducted for the outcomes presenting at least ten studies (Borenstein et al., 2009).

For both types of moderator analyses (subgroups and meta-regression), adjusted R^2 was used to examine how much of the true variance was explained by the moderators. Adjusted R^2 was calculated based on the two estimates for T^2 (variance of the true effects) using the formula: $R = 1 - \left(\frac{T^2_{within\ or\ unexplained}}{T^2_{total}}\right)$ (Borenstein et al., 2009).

Due to the limited number of studies, especially at the follow-up measurement, these analyses were conducted for the longest period of assessment available (post-treatment or follow-up).

Sensitivity analyses

Sensitivity analyses were carried out to explore whether treatment effects were affected by methodological quality and risk of bias. The effect of total methodological quality on the magnitude of the effect size was analyzed by means of meta-regression (using the aforementioned approach). Publication bias was examined using the following approaches: 1) visual inspection of funnel plot for asymmetry; 2) Egger's test (Sterne & Egger, 2001) to confirm the visual impression; and 3) Duval and Tweedie's 'trim and fill' method (Duval & Tweedie, 2000), which allows the estimation of an adjusted effect size taking into account possible missing studies.

To confirm the validity of the results obtained, primary analyses were repeated excluding 1) studies presenting a high/uncertain risk of bias across categories, 2) studies presenting less strict diagnostic criteria (e.g. persistent fatigue for less than 6 months), and 3) studies in which the intervention and comparison conditions included additional pharmacological treatment for CFS.

Results

Description of included studies

A total of 214 potentially relevant articles (after removing duplicates) were identified in the literature search and additional hand searches. After the screening of titles and abstracts 168 studies were excluded. The remaining 46 eligible studies were reviewed, which resulted in the inclusion of 26 studies reporting on 16 trials in the present meta-analysis (*see* Figure 1; references of excluded studies and reasons for exclusion are presented in Appendix B). Tables 1 and 2 show the characteristics of the trials included in the meta-analysis.

Study characteristics

Most studies were conducted in the United Kingdom (n=9) and

the Netherlands (*n*=3), in secondary-tertiary care settings (e.g. specialized CFS clinics) (n=11) or in primary care (*n*=3).

Participant characteristics

In total, 1843 participants were included in the meta-analysis, with a mean age of 39 years; approximately 75% were women. Most trials included CFS patients diagnosed according to the Oxford or/and the CDC criteria. The exceptions were (1) the study conducted by Ridsdale and colleagues (2012) targeting patients with a complaint of persistent unexplained fatigue of at least 3 months, and (2) the trial conducted by Prins, Van der Meer & Bleijenberg (2001), which included patients with ICF. In seven studies, severity of the disease, established on the basis of cut-off scores for fatigue severity and functional impairment/physical functioning scales, was an additional criterion for patient inclusion in the trial. Drop-out percentages in intervention conditions ranged from 0% (Wallman et al, 2004) to 35% in the trial conducted by Prins and colleagues (2001), which was one of the trials that lasted for a longer period of time (8 months) and consisted of a high number of sessions (16 sessions).

Outcome measures

Ten RCTs (Deale et al., 1997; Fulcher & White, 1997; Wearden et al., 1998; Powell et al., 2001; Wallman et al., 2004; Moss-Morris, Sharon, Tobin, & Baldi, 2005; O'Dowd et al., 2006; Wearden et al., 2010; White et al., 2011; Ridsdale, Hurley, King, McCrone, & Donaldson, 2012) assessed fatigue severity using the Chalder Fatigue Scale (Chalder et al., 1993). In three other trials (Prins et al., 2001; Knoop, Van der Meer, & Bleijenberg, 2008; Tummers et al., 2012) fatigue severity was assessed with the Checklist of Individual Strength (Vercoulen, Alberets, & Bleijenberg, 1999). One study (Jason et al., 2007) used the Fatigue Severity Scale (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) and another trial (Sharpe et al., 1996) used a single-item to assess fatigue.

Of the thirteen studies assessing functional impairment/physical functioning, eleven studies (Deale et al., 1997; Fulcher & White, 1997; Powell et al., 2001; Moss-Morris et al., 2005; O'Dowd et al., 2006; Jason et al., 2007; Knoop et al., 2008; Wearden et al., 2010;

Núñez et al., 2011; White et al., 2011; Tummers et al., 2012) used the Short Form Health Survey-36 (Ware & Sherbourne, 1992), one trial (Ridsdale et al., 2012) used the Work and Social Adjustment Scale (Mundt, Marks, Shear, & Greist, 2002) and another study (Prins et al., 2001) used the Sickness Impact Profile (Bergner, Bobbitt, Carter, & Gilson, 1981). Physical activity was assessed in seven trials, by means of actigraphy (Prins et al., 2001 and Knoop et al, 2008, *reported in* Wiborg, Knoop, Stulemeijer, Prins, & Bleijenberg, 2010), the six-minute walking test (Sharpe et al., 1996; Jason et al., 2007; White et al., 2011), the incremental shuttle walking test (O'Dowd et al., 2006), and a timed step test (Wearden & Emsley, 2013). Physical capacity was assessed in four trials (Fulcher & White, 1997; Moss-Morris et al., 2005; Wearden et al., 1998; Wallman et al., 2004;) by means of laboratory physical capacity measures (e.g. oxygen consumption).

Eleven studies assessed psychological distress (depression and/or anxiety). Nine of these (Fulcher & White, 1997; Wearden et al., 1998; Powell et al., 2001; Sharpe, 1996; Wallman et al., 2004; O'Dowd et al., 2006; Wearden et al., 2010; White et al., 2011; Ridsdale et al., 2012) used the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983), two RCTs (Deale et al., 1997; Jason et al., 2007) used the Beck Depression Inventory (Beck, Steer, & Brown, 1996), and the Beck Anxiety Inventory (Hewitt & Norton, 1993) was used in one trial (Jason et al., 2007).

Intervention characteristics

In six trials the intervention group received Graded Exercise Therapy (GET), which consisted of exercise prescription (aerobic activities) adapted to the patient's physical capacity assessed at baseline (e.g. 40% of $V0_2$ max) taking into account a gradual increase in the duration and intensity of aerobic activities (e.g. walking). Patients were recommended not to exceed the levels of exercise agreed upon beforehand by the therapist and patient in order to avoid overexertion, and to maintain these levels if symptoms got worse. The exception was the graded exercise program conducted by Wallman and colleagues (2004) in which patients were advised to reduce their activity levels if symptoms got worse (i.e. flexibility in physical activity levels-pacing). GET

interventions consisted of supervised aerobic exercise sessions and/or home-based exercise prescription. The number of sessions ranged from 8 to 14 sessions, lasting for 12 to 24 weeks, with the exception of one trial which had only 1 face-to-face session and 6 telephone contacts (Wallman et al., 2004). One GET trial presented a booster session after the end of the intervention (White et al, 2011). GET interventions were conducted by exercise physiologists and/or physical therapists, except in one trial (Moss-Morris et al., 2005) where the intervention was delivered by psychologists. In one of the trials both intervention and control groups included a placebo drug component (Wearden et al., 1998).

Two trials (Powell et al., 2001; Wearden et al., 2010) consisted of Pragmatic Rehabilitation, an educational treatment providing patients with an explanatory model for their symptoms (i.e. a model integrating physical deconditioning, circadian dysrhythmia and disturbed sleep patterns). The program, collaboratively established by therapist and patient, included a home-based graded exercise program, normalization of sleep patterns, and practicing rest and relaxation. The treatment also included an educational support manual. The trial conducted by Powell and colleagues (2001) was delivered by psychologists and provided minimal contact to patients, consisting of 2 face-to-face sessions and 2 brief telephone contacts (plus access to a telephone helpline), lasting for 12 weeks. The trial conducted by Wearden and colleagues (2010) was delivered by nurses, had 5 face-to-face home visits and five additional telephone contacts, lasting for 18 weeks.

In seven other trials, the intervention condition consisted of Cognitive-Behavioral Therapy (CBT) with a graded physical activity/exercise component. In general, these interventions challenge cognitions and behaviors related to the perpetuation of fatigue and aim at increasing patients' sense of control over symptoms. Patients are encouraged to engage in a gradual increase of exercise levels, sleep hygiene is addressed and patients are supported to set personal recovery goals (e.g. work). Two of these RCTs (Knoop et al., 2008; Tummers et al., 2012) were minimal contact CBT interventions, consisting of patient (self-help) CBT-based manuals (with assignments) and regular email or telephone contacts to provide feedback. In addition, these

two CBT interventions distinguished between relatively active (characterized by an alternation of over-activity and rest) and low active patients. The first group of patients was initially encouraged to balance their daily activities and rest, and both patient groups were supported to gradually increase their physical activity levels (Bleijenberg, Prins, & Bazelmans, 2003). With the exception of these two trials, the number of face-to-face CBT sessions ranged from 8 to 16 sessions, with a duration of 16 to 32 weeks. Four interventions were conducted by psychologists/psychotherapists (Sharpe, 1996; Deale et al., 1997; Prins et al., 2001; Knoop et al., 2008). Two interventions were conducted by nurses (Wearden et al., 2010; Tummers et al., 2012). Another trial was delivered by a team consisting of psychologists/ psychotherapists, physical therapists and occupational therapists (O'Dowd et al., 2006). Only one intervention was delivered in a group format (O'Dowd et al., 2006).

Finally, one study (Núñez et al., 2011) consisted of a multidisciplinary treatment (called multiconvergent thrapy), combining CBT and GET group sessions and pharmacological treatment (painkillers and non-steroidal anti-inflammatory drugs). The CBT component of this trial also included progressive muscle relaxation, assertiveness training, and memory and attention training. The GET component included aerobic exercise (walking) carried out according to the protocols and also included relaxation and flexibility training.

Control condition characteristics

The type of control conditions differed across trials. Ten RCTs compared the intervention arms against passive control groups, such as waiting list (Knoop et al., 2008; Tummers et al., 2012), or treatment as usual (Moss-Morris et al., 2005; O'Dowd et al., 2006; Powell et al., 2001; Prins et al., 2001; Ridsdale et al., 2012; Sharpe et al, 1996; Wearden et al., 2010; White et al., 2011).

The remaining six trials had active control groups, presenting a structure/format similar to the intervention arms. In two of these trials, control groups received flexibility and relaxation training, conducted either at home (Wallman et al., 2004) or in the same setting and with the same provider as the intervention arm (Fulcher

& White, 1997). In both trials, control subjects were encouraged to avoid doing other physical activities. In two other RCTs patients in the control group received relaxation training (Deale et al., 1997; Jason et al., 2007), which consisted of progressive muscle relaxation, imagery and rapid relaxation skills (e.g. breathing focus). No advice was given on rest or physical activities. In the trial conducted by Wearden and colleagues (1998) participants in the control group received an exercise placebo (advice to do physical activity when capable and to rest when needed) and a drug placebo (similar to the intervention arm). In another trial patients received advice (called exercise counseling) on doing aerobic activities and stretching exercises at home (Núñez et al., 2011).

Quality of the studies and risk of bias

Table 2 shows the quality of the trials and risk of bias (for the detailed classification of each item see Appendix C). The quality of the trials varied, with scores ranging from 29 to 51. The trial conducted by Núñez (2011) showed the lowest quality score, and presented a high or uncertain risk of bias on all criteria. In relation to attrition bias, most studies presented adequate drop-out information and inclusion. Thirteen trials reported an adequate method of concealment and ten studies did not report details on blinding of assessors.

Synthesis of results

Table 3 shows the overall results of the meta-analysis for all outcomes at post-treatment and follow-up (the forest plots are presented in Appendix D). Table 4 presents the results of the subgroup analysis for all outcomes for the longest period of assessment available.

Effects on Fatigue severity

Fatigue severity data was available for 14 trials at post-treatment (varying from 3 to 8 months after baseline) and for 9 trials at follow-up (varying from 12 to 17 months after baseline). Significant medium effect sizes were found for fatigue severity at post-treatment (g=0.62; 95% CI 0.45-0.79) and follow-up (g=0.67; 95% CI 0.37-0.96). At both assessment points, the effects varied widely

from study to study. The trial conducted by Powell et al. (2001) showed the largest effect sizes (g=1.79 and g=2.08, respectively). The standard residuals showed these values were outliers (3.22 and 3.03, respectively). The results of the overall effect sizes if this study was removed would vary within 0.09 and 0.18 from the initial point estimate, respectively, which means this study had a large impact on the overall effect at both time points. The smallest effects were found in the trial conducted by Deale and colleagues (1997) at post-treatment (g=0.28) and the trial by Ridsdale (2012) at follow-up (g=0.10).

There was evidence of moderate to high heterogeneity between trials at both assessment points (Q= 34.84, p<0.001; I^2=63%, and Q= 43.52, p<0.001; I^2=82%, respectively), indicating that the variance could not be explained by sampling error alone (Table 3). For this reason, we examined the potential moderators of variance in effect sizes for the combined post-treatment and follow-up data (k=15, g=0.66, Z=6.814, p<0.001; 95% CI 0.47-0.85; Q= 48.43, p<0.001; I^2=71%; Table 4). Interventions conducted in secondary-tertiary settings, interventions delivered by psychologists or psychotherapists, and interventions providing minimal contact (versus more intensive contact), showed higher effects upon fatigue severity (p=0.01, p<0.05, p<0.05, respectively) and explained 38%, 33% and 20% of the variance in fatigue severity, respectively. In addition, the overall effect sizes for interventions containing a psychological component and allowing flexibility in physical activity levels/goals were larger, but also presented high levels of heterogeneity (Table 4).

Effects on Functional impairment/physical functioning

Eleven trials at post-treatment (3-8 months) and eight trials at follow-up (12-17 months) presented data for the effects of interventions on functional impairment/physical functioning (Table 3). Combined effect sizes were g=0.30 (95% CI 0.14-0.46) at post-treatment and g=0.39 (95% CI 0.13-0.66) at follow-up. At both assessment points, the effects varied widely from study to study. The trial conducted by Deale et al. (1997) showed the largest effect sizes at both assessment points (g= 0.92 and g=1.35, respectively). At follow-up, the standard residual of this trial revealed it was

an outlier (2.32). If removed the overall effect size would drop to g=0.29. The trial conducted by O'Dowd et al. (2006) showed negative effects (g= -0.20) at post-treatment and the trial conducted by Núñez and colleagues (2011) showed a negative effect (g= -0.10) at follow-up.

The results for functional impairment/physical functioning showed evidence of moderate to high heterogeneity between trials (Q= 22.67, p<0.05; I^2=56% and Q= 30.45, p<0.001; I^2=77%, respectively). Subsequent subgroup and meta-regression analyses were conducted for the longest period of assessment available (k=13, g=0.36, Z=4.28, p<0.001; 95% CI 0.19-0.52; Q= 30.04, p<0.05; I^2=60%). There were no significant associations between study characteristics and the effect sizes of the interventions (Table 4), indicating that none of the variance in the treatments effects on functional impairment/physical functioning was explained by the moderators analyzed (adjusted R^2=0%).

Effects on Physical activity and Physical capacity

The overall effect size for physical activity at post-treatment was not significant (k=4, 5-8 months; g=0.11; 95% CI -0.07-0.28). The trial by Sharpe et al. (1996) showed the largest and the only significant effect size (g=0.63) on physical activity, with a standard residual of 2.13. If removed, overall effect size would drop to g=0.04. At follow-up, we found a significant small effect size (k=5, 12-17 months; g=0.41; 95% CI 0.25-0.57; Table 3). At follow-up, the trial of Sharpe et al. (1996) showed the largest effect size (g= 0.73) and the trial by Wearden et al (2010) the lowest effect (g=0.11). There was considerable heterogeneity between trials at post-treatment (Q=4.64, p=0.20; I^2=35%) and no evidence of heterogeneity at follow-up (Q=4.52, p=0.34; I^2=11%). The overall effect size for physical capacity at post-treatment was small but significant (k=4, 3-6 months; g=0.27; 95% CI 0.00-0.54). There was evidence of heterogeneity between trials (Q= 10.90, p<0.01; I^2=73%). The trial conducted by Moss-Morris et al. (2005) showed a negative effect (g= -0.97), that is considered an outlier effect (standard residual: -3.27). If this trial was removed, the overall effect would increase to g=0.43.

In order to conduct moderator analyses, data for both physical

activity and physical capacity at the longest available period of assessment were combined. Combining physical activity and physical capacity assessments resulted in a small but significant effect size with moderate heterogeneity between trials (k=11, g=0.27, Z=2.64, p<0.01; 95% CI 0.07-0.48; Q= 27.19, p<0.01; I^2=63%). Due to the limited number of trials, subgroup comparisons were conducted only for the following characteristics: 1) type of control group, 2) presence of a psychological component and 3) flexibility in physical activity/exercise program. There were no significant associations between these characteristics and the effect size of the interventions upon physical activity/physical capacity, indicating that none of the variance in this combined outcome variable was explained by these characteristics (adjusted R^2=0%).

Effects on Depression

Data was available for ten trials at post-treatment (3-6 months) and seven trials at follow-up (12-17 months). Overall, interventions yielded significant effect sizes on depression levels at post-treatment (g=0.41; 95% CI 0.22-0.59) and follow-up (g=0.36; 95% CI 0.14-0.58). At both assessment points, the trial conducted by Powell et al. (2001) showed the largest effect sizes (g=0.93 and g=1.12, respectively). At follow-up, the standard residual of this trial was 2.41. The overall effect, if this study was removed, decreased to g=0.25. At post-treatment the smallest effect sizes were found in the trial conducted by Fulcher and colleagues (1997) (g=0.03), in which patients were excluded at baseline if presenting a psychiatric disorder. If removed the overall effect would increase to g=0.44. At follow-up, the smallest effect was found for the trial conducted by Jason et al (2007) (g=0.08).

For depression there was evidence of considerable heterogeneity between studies (Q=16.56, p=0.06; I^2=46%, and Q=13.17, p=0.04; I^2=54%, respectively) (Table 3). Subsequent subgroup analyses and meta-regression analyses were conducted for the longest available period of assessment (k=12, g=0.35, Z=3.84, p<0.001; 95% CI 0.17- 0.54; Q= 27.19, p<0.001; I^2=68%). There were no significant moderator effects for type of control condition, type of setting and presence of a psychological component. Interventions with minimal direct patient-provider contact had significantly higher

effects upon depression (p=<0.001), explaining 52% of the variance in depression. In addition, meta-regression showed a marginal association between depression and length of the intervention (slope: -0.03, Z=-1.67, p=0.10). Furthermore, there was a marginal moderator effect for flexibility in physical activity levels (p<0.10; adjusted R^2=9%).

Effects on Anxiety

Small but significant effects were found for anxiety at post-treatment (k=7, 3-6 months; g=0.28; 95% CI 0.13-0.43) and follow-up (k=6, 12-17 months; g=0.22; 95% CI 0.08-0.37) (see Table 3). At post-treatment, the trial conducted by Wallman et al. (2004) showed the largest effect size (g=0.57) and the trial by Wearden and colleagues (1998) showed the smallest (g=0.12). At follow-up, the trial conducted by Powell and colleagues (2001) showed the largest effect size (g=0.52) and the smallest effect was found in the trial conducted by Sharpe et al (1996) (g=0.07). There was no evidence of heterogeneity between the trials on both assessment points (Q= 2.70, p=0.85; I^2=0% and Q= 2.29, p=0.81; I^2=0%, respectively). For that reason, no further moderator analyses were conducted.

Sensitivity analyses

Meta-regressions with respect to methodological quality did not reveal any significant slope for any of the outcomes assessed (Table 4). Visual inspection of the funnel plots revealed asymmetry for fatigue severity. Egger's test did not show a significant asymmetric funnel plot at post-treatment (intercept: 2.54, 95% CI -0.41-5.48, p=0.09). After adjustment with the trim-and-fill procedure the magnitude of the effect sizes decreased from g=0.62 to g=0.47 at post-treatment (95% CI 0.28-0.66; number of trimmed studies=4). At follow-up, inspection of the funnel plot for fatigue severity showed the presence of asymmetry, although Egger's test did not indicate a significant asymmetric plot (intercept: 3.81, 95% CI -1.56-9.15, p=0.17). After adjustment the point estimate dropped from g=0.67 to g=0.46 (95% CI -0.12-0.80; number of trimmed studies= 2). Furthermore, inspection of the funnel plot of the effects for physical impairment/functioning at post-treatment revealed the presence of asymmetry. Egger's test showed a marginal

significant asymmetric funnel plot (intercept: 1.01, 95% CI -2.80-4.84, p=0.56). After adjustment with the trim-and-fill procedures, the magnitude of the effect dropped from g=0.30 to g=0.24 (95% CI 0.07-0.41, number of trimmed studies=2). We also found presence of asymmetry for physical capacity at post-treatment. Egger's test indicated an asymmetric funnel plot (intercept: -8.79, 95% CI -17.31 – 0.28, p=0.05). After adjustment the point estimate dropped from g=0.27 to g=0.18 (95% CI -0.06-0.42, number of trimmed studies=1). There was no indication of asymmetry for other outcomes.

Primary analyses were repeated with the exclusion of the trial by Nuñez (2011), which presented a high risk of bias, poor methodological quality (table 2) and included additional pharmacological treatment in the intervention arm. Excluding this study led to an increase in the magnitude of treatment effects for functional impairment/physical functioning at follow-up from g=0.39 to g=0.47. Analyses were also repeated with the exclusion of the trial by Jason (2007) due to high/uncertain risk of bias in all categories. Excluding this trial led only to very small increases in the overall point estimates between 0.02 (physical activity) to 0.03 (depression). The exclusion of the trial conducted by Ridsdale (2012) because of less restrictive diagnostic criteria (complaint of fatigue for more than 3 months), led to an increase in the overall point estimate for fatigue severity at follow-up (from g= 0.67 to g=0.74), and to increases of approximately 0.03 for the other outcomes.

Discussion

This meta-analysis examined the effectiveness of behavioral and psychological treatments focusing on graded aerobic physical activity/exercise in chronic fatigue patients. Treatments included Graded Exercise Therapy (GET), Cognitive behavioral Therapy (CBT), pragmatic rehabilitation and multicomponent approaches. Sixteen trials assessing fatigue severity, physical functioning /functional impairment, physical activity/physical capacity, and/or psychological distress (depression and anxiety) at post-treatment and/

or follow-up, were included. In addition, this meta-analysis analyzed the potential moderating effects of the following trial characteristics: care provided to the control condition, treatment setting, provider of the treatment, length of treatment, whether the intervention included a psychological component (or not), flexibility in setting physical activity levels or goals in accordance with the patients' exercise tolerance, and whether or not the intervention was a minimal (direct face to face) contact intervention.

Our results indicate that interventions focusing on graded physical activity/exercise have beneficial effects on chronic fatigue management, which is in accordance with the results from previous reviews (Edmonds et al., 2004; Malouff et al., 2008; Price et al., 2008; Castell et al., 2011). Interventions had a moderate impact on fatigue severity at post-treatment (g=0.62) and at follow-up (g=0.67). The post-treatment result obtained was somewhat similar to the results found in the Malouff study (2008) [Physical fatigue: d=0.81; mixed (physical and mental) fatigue: d= 0.52], and higher than the effect sizes reported by Castell et al (2011; GET: g= 0.41; CBT: g=0.36) Treatment effects varied widely between studies and subsequent subgroup comparisons revealed that several trial characteristics were significant moderators of the effect of the interventions on fatigue severity. Interventions conducted in secondary-tertiary settings had a higher effect on fatigue severity reduction than interventions conducted at primary care. Castell (2011) also found the lowest intervention effect in primary care trials. It is however important to point out that of the studies included in our meta-analysis, only three studies were conducted in primary care settings, each of them with clearly distinct features. One trial, the Pragmatic Rehabilitation trial, was conducted by nurses who did home visits (Wearden et al., 2010), another was a GET trial conducted by physical therapists (Ridsdale et al., 2012), and the last one was a CBT trial with a graded exercise component delivered by several health care specialists to groups of patients (O'Dowd et al., 2006). Interventions delivered by psychologists or psychotherapists were more effective in reducing fatigue severity, although heterogeneity within this subgroup was high. Previous meta-analyses did not examine this moderator effect. Finally,

minimal contact self-management interventions, consisting of a maximum of 3 face-to-face sessions, providing additional remote guidance and in many cases including patient (self-help) manuals, were associated with larger effects on fatigue severity. This result is in line with recent research that pointed at the beneficial effects of minimal contact interventions on psychological (Haug et al., 2012) and physical symptoms (Pajak et al., 2013). Furthermore, in a recent trial directly comparing CBT delivered face-to-face to CBT delivered by telephone (with an initial face-to- face session), similar beneficial effects were found on fatigue, social adjustment and physical functioning in CFS/ME patients (Burgess, Andiappan, & Chalder, 2012).

Regarding physical functioning/functional impairment, there were small treatment effects at both assessment points (g=0.30 and g=0.39), which is in line with the results from a previous meta-analysis (e.g. Castell et al., 2011). Again, we found that intervention effects varied widely between studies and that some interventions had no significant effects on physical functioning/functional impairment. None of the moderators explained the observed variance in treatment effect.

This is the first meta-analysis assessing the impact of interventions with a graded activity/exercise component on physical activity and physical capacity. We found few studies reporting on the effects of interventions on physical activity/ capacity. At post-treatment, interventions had a trivial effect on physical activity (g=0.11) and a small effect on physical capacity at post-treatment and (g= 0.27). At follow-up, overall effect on physical activity was of small magnitude (g=0.41). None of the moderators explained the observed variance in treatments effect. However, due to the limited number of studies, these analyses were only conducted for some of the potential moderators. One of the possible reasons for the small effects found may be the heterogeneous measurement of physical activity/physical capacity. Some studies made use of actigraphy, while others relied on walking tests or on physiological measures.

The small effect of existing (psychological and behavioural) interventions targeting physical activity and physical capacity may point at the fact that alternative ways of promoting physical activity,

e.g. making use of motivational counseling and self-regulation approaches (e.g. Janssen, De Gucht, van Exel, & Maes, 2013) may be more succesful in changing this health behaviour. The discrepancy that was found in this meta-analysis between the effects found for fatigue severity and for physical activity could indicate that the mere increase of physical activity does not necessary lead to improved outcomes in terms of chronic fatigue management. Flexibility in physical activity levels or goals combined with pacing (balance between activities and rest) may be equally important for chronic fatigue management (Nijs et al., 2008). It could also be hypothesized that the effect of the interventions on fatigue cannot be explained by changes in physical activity and/or physical capacity. This hypothesis is in accordance with a study conducted by Wiborg (Wiborg et al., 2010) that examined whether (changes in) physical activity mediated the effect of CBT on fatigue in three separate trials. CBT interventions reduced fatigue, but did not have an effect on physical activity. As a consequence, no mediation effect of physical activity was found.

For depression, small effect sizes were found at both assessment points (g=0.41 and g=0.32), slightly higher than the effect sizes found in previous reviews (Edmonds, 2004; Castell et al, 2011). Interventions with minimal face to face contact were associated with larger effect sizes, and a marginal significant effect was found for the length of the intervention. Interventions that allowed for flexibility in physical activity levels presented higher effects on depresion. Finally, small effect sizes were found for anxiety at both assessment points (g=0.28 and g=0.22). The magnitude of the effects is higher than what was found in a previous meta-analysis (Castell et al., 2011; GET: g= 0.01; CBT: g=0.15). Our results should however be interpreted with care as only a small number of studies were included in the analyses for anxiety at both assessment points. It may be the case that patients with more severe psychological distress or co-existing mood disorders will benefit more from additional emotional regulation approaches (e.g. CBT for mood disorders). In fact, two recent trials have found that depressive symptoms were a significant moderator of treatment effects (Tummers, Knoop, van Dam & Bleijenberg, 2013; Wearden, Dunn, Dowrick, & Morriss, 2012). Future reviews could address

the potential moderator effect of psycholological distress in a wide range of trials.

For all outcomes, heterogeneity in effect sizes was not associated with type of care provided to the control condition (passive vs. active) as was found in previous meta-analyses (Malouff et al, 2008; Castell et al, 2011). Similarly, a flexible approach to physical activity levels or goals was not significantly associated with higher effect sizes, except for the marginal effect found for depression. We did not find a significant difference in effects between interventions focusing only on physical activity or also containing a psychological component, but results point to a greater effect of this last type of treatment on both fatigue and depression. Finally, heterogeneity in treatment effects was not associated with the length of treatment for any of the outcomes.

Limitations and suggestions for future research

The present meta-analysis has a number of limitations. First, although interventions have shown beneficial effects for most outcomes, we found a high level of heterogeneity between studies that could not be (fully) accounted for by the moderators that we examined. The limited number of trials included in this review limits the conclusions that can be drawn from the moderator analyses, because non-significant effects may be due to low statistical power (Borenstein et al., 2009). Future studies should continue to explore other potential moderators that can account for differences between trial results. Among these are patient and disease-related characteristics (e.g. illness duration, severity of disease, mood disorders, avoidance or all-or-nothing behaviors), treatment features (e.g. physical activity, flexible graded activity + pacing) or design-related moderators such as single-centre vs. multi-centre trials.

Second, sensitivity analysis revealed some indication of publication bias for the outcomes fatigue severity, physical functioning and physical capacity. The existence of unpublished trials with negative results could have reduced the effect sizes for some of the outcomes analyzed. Adjusted effect sizes and re-analysis excluding trials with low methodological quality, did not alter the significance of the effect sizes, with the

exception of physical capacity. In addition, the sample size of many trials included in this meta-analysis was small, which constitutes a methodological limitation (Borenstein et al., 2009).

Third, promising recent trials adopting a multidisciplinary rehabilitation treatment approach, could not be included because they were non-randomized and/or did not provide enough statistical information. The only study on multidisciplinary rehabilitation that was included (Núñez et al., 2011) was characterized by poor methodological quality.

Fourth, most of the coding of intervention characteristics was based on the intervention description provided in the articles. In many cases these descriptions were limited, and e.g. did not present enough information regarding the behavior change techniques used. For this reason, we were not able to explore the moderating effect of behavior change techniques (e.g. use of self-regulation strategies such as goal setting). The same accounts for the description of the content of manuals that were used in different interventions. Future studies should give a sufficiently detailed account of the content of the intervention/self-help manual offered to patients.

Fifth, although we compared our results to the results of previous meta-analyses, this comparison is hampered by a number of differences related to the focus of the meta-analysis as well as the statistical procedures that were followed. More in particular, this meta-analysis (1) included recently published studies that were not included in previous meta-analyses, (2) did not include studies targeting children/youth with chronic fatigue, (3) was conducted separately for each outcome at post-treatment and follow-up, (4) compared activity based interventions to interventions with an additional psychological component, which was not limited to CBT, and (5) as Castell previously stated (2011) different procedures for calculating effect sizes may have been adopted based on the information provided in the original trials included in this meta-analysis.

Sixth, although most outcomes were assessed using validated self-report scales, the way scores were calculated was not always clear. Future randomized controlled trials should pay more attention to the way statistical data are presented, making an effort to present effect sizes and raw data (means and standard deviations) for all outcomes, trial arms and assessment periods.

Seventh, the number of studies included in this meta-analysis that

presented follow-up data (without crossovers) was limited and only available for a maximum period of 17 months. Hence, although these interventions seem to lead to sustainable beneficial effects on chronic fatigue management (Malouff et al, 2008), more research is needed to understand long-term effects as well as the potential mechanisms contributing to the maintenance of self-management behaviors.

Finally, future studies should also examine the effect of interventions on additional outcomes (e.g. recovery rate), and compare different treatment formats (telephone, web-based, face to face).

Conclusion

This meta-analysis of behavioral and psychological interventions targeting graded activity suggests that these interventions have sustained beneficial effects on chronic fatigue management, in particular on fatigue severity reduction for which a medium effect was found. The finding that minimal contact interventions have similar and in some cases higher effects on fatigue severity and depression compared to more intensive interventions is important as these interventions can be more easily implemented in standard health care, can be useful for patients presenting difficulties in regularly attending health care facilities (Burgess et al., 2012), and can be suitable for patients who do not need more intensive forms of treatment (Tummers et al., 2012). All trials included in this meta-analysis had an initial face to face contact with patients, which may have led to increased motivation of patients to engage in a behavior change process (Burgess et al., 2012). Most of these minimal interventions also included patient (self-help) manuals and allowed flexible physical activity/exercise levels that take into consideration the patients' own resources, which can add to chronic fatigue management. Notwithstanding the beneficial effects of the behavioral and psychological interventions included in this meta-analysis and the valuable indications about targets and format of future interventions, more research is needed to identify optimal features of interventions for chronic fatigue management.

Acknowledgements

This study was partially funded by the Portuguese Foundation for Science and Technology with a grant to the first author (SFRH/BD/47579/2008).

The authors would like to thank Andreia Cordeiro for her assistance with the bibliographic search and screening of tittles and abstracts.

References

* (studies included in this systematic-review and meta-analysis)

Afari, N., & Buchwald, D. (2003). Chronic Fatigue Syndrome: A Review. *Am J Psychiatry, 160*, 221-236. doi: 10.1176/appi.ajp.160.2.221.

Ahl, A., Mikocka-Walus A., Gordon A. &Andrews J.M. (2013). Are self-administered or minimal therapist contact psychotherapies an effective treatment for irritable bowel syndrome(IBS): A systematic review. *Journal of Psychosomatic Research, 75,* 113-120. doi: 10.1016/j.jpsychores.2013.04.008

APA Publications and Communications Board Working Group on Journal Article Reporting Standards (2008).Reporting Standards for Research in Psychology: Why Do We Need Them? What Might They Be? *Am Psychol, 63,* 848-849.

Beck, A. T., Steer, R. A., & Brown, G. (1996). *Manual for the Beck Depression Inventory–II*. San Antonio Texas: Psychological Corporation.

*Bentall, R. P., Powell, P., Nye, F. J., & Edwards, R. H. T. (2002). Predictors of response to treatment for chronic fatigue syndrome. *The British Journal of Psychiatry, 181*(3), 248-252.doi: 10.1192/bjp.181.3.248

Bergner, M., Bobbitt, R. A., Carter, W. B., & Gilson, B. S. (1981). The Sickness Impact Profile: development and final revision of a health status measure. *Med Care, 19*(8), 787-805.

Bleijenberg, G., Prins, J., & Bazelmans, E. (2003). Cognitive-behavioral therapies. In L. A. Jason, P. A. Fennell & R. R. Taylor (Eds.), *Handbook of Chronic Fatigue Syndrome*. New Jersey: Wiley.

Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. (2005). Comprehensive Meta-Analysis Version 2. Engelwood, NJ: Biostat.

Borenstein, M., Hedges, L. V., Higgins, J., & Rothstein, H. R. (2009). *Introducton to Meta-analysis*. Chichester, United Kingdom: Wiley & Sons, Lda.

Burgess, M., Andiappan, M., & Chalder, T. (2012). Cognitive Behaviour Therapy for Chronic Fatigue Syndrome in Adults: Face to Face versus Telephone Treatment - A Randomized Controlled Trial. *Behavioural and Cognitive Psychotherapy, 40*(02), 175-191. doi:10.1017/S1352465811000543.

Cairns, R., & Hotpof, M. (2005). Prognosis of chronic fatigue syndrome: a systematic review. *Occup Med, 55*, 20 -31.

Carruthers, B. M., van de Sande, M. I., De Meirleir, K. L., Klimas, N. G., Broderick, G., Mitchell, T.,...,Stevens, S. (2011). Myalgic encephalomyelitis: International Consensus Criteria. *Journal of Internal Medicine, 270*(4), 327-338. doi: 10.1111/j.1365-2796.2011.02428.x

Castell, B.D., Kazantsis, N. & Moss.Morris, R. (2011). Cognitive Behavioral Therapy and Graded Exercise for Chronic Fatigue Syndrome: A Meta-Analysis. *Clinical Psychology Science and Practice, 18*(4), 311-324. doi: 10.1111/j.1468-2850.2011.01262.x

Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., & Wallace, E. P. (1993). Development of a fatigue scale. *J Psychosom Res, 37*, 147-153. doi: 10.1016/0022-3999(93)90081-P

Clark, L., Clark, P., & White. (2005). The role of deconditioning and therapeutic exercise in chronic fatigue syndrome (CFS). *Journal of mental health, 14*(3), 237-252. doi:10.1080/09638230500136308

Cochran, W. G. (1954). The combination of estimates from different experiments. *Biometrics, 10*.

Cohen, J. (1992). A power primer. *Psychol Bull, 112*(1), 155-159.

Cox, D. L. (1999). Chronic Fatigue Syndrome – an occupational therapy programme. *Occupational Therapy International, 6*(1), 52-64. doi: 10.1002/oti.88

Cuijpers, P., Donker, T., van Strale, A., Li, J. & Andersson, G. (2010). Is guided self-help as efective as face-to-face psychotherapy for depression and anxiety disorders? A systematic review and meta-analysis fo comparitive outcome studies. *Psychological Medicine, 21*, 1-15. doi: 10-1017/S0033291710000772

*Deale, A., Chalder, T., Marks, I., & Wessely, S. (1997). Cognitive behaviour therapy for the chronic fatigue syndrome: A randomized controlled trial. *Am J Psychiatry, 154*, 408-414.

*Deale, A., Huasain, K., Chalder, T., & Wessely, S. (2001). Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: A 5-year follow-up study. *American Journal of Psychiatry,159,* 2038-2042. doi: 10.1176/appi.ajp.158.12.2038

Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics, 56*(2), 455-463.

Edmonds, L., McGuire, L., & Price, J. (2004). Exercise Therapy for

Chronic Fatigue Syndrome. *Cochrane Database Syst Rev, 3*, CD003200.

Fukuda, K., Strauss, S., Hickie, I., Sharpe, M., Dobbins, J., & Komaroff, A. (1994). The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med, 121*, 953 - 959.

*Fulcher, K., & White, P. (1997). Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ, 314*(7095), 1647 - 1652. doi:10.1136/bmj.314.7095.1647

Fulcher,K. & White, P. (1998). Chronic Fatigue Syndrome: A description of graded exercise treatment. *Physiotherapy*, *84*(5), 223-226. doi:10.1016/S0031-9406(05)65554-X.

Fulcher, K., & White, P. (2000). Strength and physiological response to exercise in patients with chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry, 69*, 302 - 307. doi:10.1136/jnnp.69.3.302

Haug, T., Nordgreen, T., Ost, L. G., & Havik, O. E. (2012). Self-help treatment of anxiety disorders: a meta-analysis and meta-regression of effects and potential moderators. *Clin Psychol Rev, 32*(5), 425-445. doi: 10.1016/j.cpr.2012.04.002

Hedges, L. V. (1981). Distribution Theory for Glass's Estimator of Effect size and Related Estimators. *J of Educ Behav Stat, 6*(2), 107-128.

Hewitt, P. L., & Norton, G. R. (1993). The Beck Anxiety Inventory: A psychometric analysis. *Psychological Assessment, 5*(4), 408-412. doi: 10.1037/1040-3590.5.4.408

Higgins, J., Altman, D., Gotzche, P., Juni, P., Moher, D., Oxman, A., ... Sterne, J. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ, 343*, d5928. doi: 10.1136/bmj.d5928

Holmes, G. P., Kaplan, J. E., Gantz, N. M., Komaroff, A. L., Schonberger, L. B., Straus, S. E., . . . Brus, I. (1988). Chronic Fatigue Syndrome: A Working Case Definition. *Annals of Internal Medicine, 108*(3), 387-389. doi: 10.7326/0003-4819-108-3-387

Janssen, V., Gucht, V., Exel, H., & Maes, S. (2013). A self-regulation lifestyle program for post-cardiac rehabilitation patients has long-term effects on exercise adherence. *J of Behavioral Medicine*, 1-14. doi:10.1007/s10865-012-9489-y

*Jason, L. A., Torres-Harding, S., Friedberg, F., Corradi, K., Njoku, M. G., Donalek, J., . . . Papernik, M. (2007). Non-pharmacologic interventions for CFS: A randomized trial. *Journal of Clinical*

Psychology in Medical Settings, 14(4), 275-296. doi: 10.1007/s10880-007-9090-7

Julian, P. T. H., Simon, G. T., Jonathan, J. D., & Douglas, G. A. (2003). Measuring inconsistency in meta-analyses. *BMJ, 327*. doi:10.1136/bmj.327.7414.557

*Knoop, H., Van der Meer, J., & Bleijenberg, G. (2008). Guided self-instructions for people with chronic fatigue syndrome: a randomised controlled trial. *Br J Psychiatry, 190*, 340 - 341. . doi: 10.1192/bjp.bp.108.051292.

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol, 46*(10), 1121-1123.

Lackner, J. M., Mesmer, C., Morley, S., Dowzer, C., & Hamilton, S. (2004). Psychological Treatments for Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis. *Journal of Consulting and Clinical Psychology, 72*(6), 1100-1113. doi: 10.1037/0022-006X.72.6.1100

Lehman, A. M., Lehman, D. R., Hemphill, K. J., Mandel, D. R., & Cooper, L. M. (2002). Illness experience, depression, and anxiety in chronic fatigue syndrome. *Journal of psychosomatic research, 52*(6), 461-465.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., . . . Moher, D. (2009). The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLoS Med, 6*, e1000100. doi:10.1136/bmj.b2700

Malouff, J. M., Thorsteinsson, E. B., Rooke, S. E., Bhullar, N., & Schutte, N. S. (2008). Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: A meta-analysis. *Clinical Psychology Review, 28*(5), 736-745. doi: 10.1016/j.cpr.2007.10.004

Moncrieff, J., Churchill, R., Drummond, D. C., & McGuire, H. (2001). Development of a quality assessment instrument for trials of treatments for depression and neurosis. *International Journal of Methods in Psychiatric Research, 10*(3), 126-133. doi: 10.1002/mpr.108

*Moss-Morris, R., Sharon, C., Tobin, R., & Baldi, J. (2005). A randomized controlled graded exercise trail for chronic fatigue syndrome: outcomes and mechanisms of change. *J Heal Psychol, 10*(2), 245 -

259. doi: 10.1177/1359105305049774
Mundt, J. C., Marks, I. M., Shear, M. K., & Greist, J. H. (2002). The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *Br J Psychiatry, 180*, 461-464. doi:10.1192/bjp.180.5.461
National Institute for Health and Clinical Excellence (2007). *NICE clinical guideline 53. Chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy): diagnosis and management of CFS/ME in adults and children*.
Nijs, J., Paul, L., & Wallman, K. (2008). Chronic fatigue syndrome: an approach combining self-management with graded exercise to avoid exacerbations. *J Rehabil Med, 40*, 241 - 247. doi: 10.2340/16501977-0185.
Nijs, J., Aelbrecht, M., Meeus, J., Van Oosterwijck, E., Zinzen, P., & Clarys, P. (2011a). Tired of being inactive: a systematic literature review of physical activity, physiological exercise capacity and muscle strength in patients with chronic fatigue syndrome. *Disability and rehabilitation, 33*(17-18), 1493-1500. doi: 10.3109/09638288.2010.541543.
Nijs, J., Wallman, K., & Paul, L. (2011b). Chronic Fatigue Syndrome. In J. M. Saxton (Ed.), *Exercise and Chronic Disease: An Evidence-Based Approach*. New York, USA: Routledge.
*Núñez, M., Fernández-Solà, J., Nuñez, E., Fernández-Huerta, J.-M., Godás-Sieso, T., & Gomez-Gil, E. (2011). Health-related quality of life in patients with chronic fatigue syndrome: group cognitive behavioural therapy and graded exercise versus usual treatment. A randomised controlled trial with 1 year of follow-up. *Clinical Rheumatology, 30*(3), 381-389. doi: 10.1007/s10067-010-1677-y
*O'Dowd, H., Gladwell, P., Rogers, C. A., Hollinghurst, S., & Gregory, A. (2006). Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme. *Health Technol Assess, 10*(37), iii-iv, ix-x, 1-121.
Pajak, R., Lackner, J., & Kamboj, S. K. (2013). A systematic review of minimal-contact psychological treatments for symptom management in Irritable Bowel Syndrome. *Journal of psychosomatic research, 75*(2), 103-112. .doi: 10.1016/j.jpsychores.2013.05.007.
*Powell, P., Bentall, R., Nye, F., & Edwards, R. (2001). Randomised controlled trial of patient education to encourage graded exercise

in chronic fatigue syndrome. *BMJ, 322*, 387. doi: 10.1136/bmj.322.7283.387

*Powell, P., Bentall, R., Nye, F., & Edwards, R. (2004). Patient education to encourage graded exercise in chronic fatigue syndrome: 2-year follow-up of randomised controlled trial. *The British Journal of Psychiatry, 184*(2), 142-146. doi:10.1192/bjp.184.2.142

Price, J., Mitchell, E., Tidy, E., & Hunot, V. (2008). Cognitive behaviour therapy for chronic fatigue syndrome in adults. *Cochrane Database Syst Rev, 3*, CD001027.

Prins, J., Van der Meer, J., & Bleijenberg, G. (2006). Chronic fatigue syndrome. *Lancet, 367*, 346 - 355.

*Prins, J. B., Bleijenberg, G., Bazelmans, E., Elving, L. D., de Boo, T. M., Severens, J. L., ... van der Meer, J. W. M. (2001). Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *The Lancet, 357*(9259), 841-847. doi: http://dx.doi.org/10.1016/S0140-6736(00)04198-2

Ranjith, G. (2005). Epidemiology of chronic fatigue syndrome. *Occupational Medicine, 55*(1), 13-19. doi: 10.1093/occmed/kqi012

*Ridsdale, L., Hurley, M., King, M., McCrone, P., & Donaldson, N. (2012). The effect of counselling, graded exercise and usual care for people with chronic fatigue in primary care: a randomized trial. *Psychological Medicine, 42*(10), 2217-2224. doi:10.1017/S0033291712000256.

Sabes-Figuera, R., McCrone, P., Hurley, M., King, M., Donaldson, A., & Ridsdale, L. (2010). The hidden cost of chronic fatigue to patients and their families. *BMC Health Services Research, 10*(1), 56. doi:10.1186/1472-6963-10-56

Sharpe, M. C. (1991). A Report-Chronic Fatigue Syndrome: Guidelines for Research. *Journal of the Royal Society of Medicine, 84*(2), 118-121.

*Sharpe, M., Hawton, K., Simkin, S., Surawy, C., Hackmann, A., Klimes, I.,... Seagroatt, V. (1996). Cognitive behaviour therapy for the chronic fatigue syndrome: a randomized controlled trial. BMJ, 312, 22-26. doi:10.1136/bmj.312.7022.22

Sterne, J. A. C., & Egger, M. (2001). Funnel plots for detecting bias in meta-analysis: Guidelines on choice of axis. *Journal of clinical epidemiology, 54*(10), 1046-1055.

Thomas, M. A., Sadlier, M. J., & Smith, A. P. (2008). A multiconvergent approach to the rehabilitation of patients with chronic fatigue

syndrome: a comparative study. *Physiotherapy, 94*(1), 35-42. doi: 10.1016/j.physio.2007.04.013

*Tummers, M., Knoop, H., & Bleijenberg, G. (2010). Effectiveness of stepped care for chronic fatigue syndrome: a randomized noninferiority trial. *J Consult Clin Psychol, 78*(5), 724-731. doi: 10.1037/a0020052

*Tummers, M., Knoop, H., van Dam, A., & Bleijenberg, G. (2012). Implementing a minimal intervention for chronic fatigue syndrome in a mental health centre: a randomized controlled trial. *Psychological Medicine, 42*(10), 2205-2215.

*Tummers, M., Knoop, H., van Dam, A., & Bleijenberg, G. (2013). Moderators of treatment response to guided self-instructions for chronic fatigue syndrome. *Journal of Psychosomatic Research, 74*(5), 373-377. doi: 10.1017/S0033291712000232.

Vercoulen, J., Alberets, M., & Bleijenberg, G. (1999). De Checklist Individual Strenght (CIS). *Gedragstherapie, 32*, 31 - 36.

Vos-Vromans, D. C., Smeets, R. J., Rijnders, L. J., Gorrissen, R. R., Pont, M., Koke, A. J., . . . Knottnerus, A. (2012). Cognitive behavioural therapy versus multidisciplinary rehabilitation treatment for patients with chronic fatigue syndrome: study protocol for a randomised controlled trial (FatiGo). *Trials, 13*(1), 71. doi:10.1186/1745-6215-13-71

*Wallman, K. E., Morton, A. R., Goodman, C., Grove, R., & Guilfoyle, A. M. (2004). Randomised controlled trial of graded exercise in chronic fatigue syndrome. *Medical Journal of Australia, 180*(9), 444-448.

*Wallman, K. E., Morton, A. R., Goodman, C. & Grove, R.(2005) Reliability of physiological, psychological, and cognitive variables in chronic fatigue syndrome. *Research in Sports Medicine: An international journal, 13(3)*, 231-241. doi: 10.1080/15438620500222562

Ware, J. E., & Sherbourne, C.D. (1992). The MOS 36-item short-form health survey (SF-36). Conceptual framework and item selection. *Med Care, 30*(6), 473-483.

*Wearden, A. J., Morriss, R. K., Mullis, R., Strickland, P. L., Pearson, D. J., Appleby, L., . . . Morris, J. A. (1998). Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *Br J Psychiatry, 172*, 485-490. doi:10.1192/bjp.172.6.485

*Wearden, A. J., Riste, L., Dowrick, C., Chew-Graham, C., Bentall, R. P., Morriss, R. K., . . . Powell, P. (2006). Fatigue Intervention by Nurses Evaluation - The FINE Trial. A randomised controlled trial of nurse led self-help treatment for patients in primary care with chronic fatigue syndrome: study protocol. . *BMC Medicine, 4*(1), 9. doi:10.1186/1741-7015-4-9

*Wearden A.J., Dowrick C., Chew-Graham C., Bentall R.P.,..., Dunn G. (2010). Nurse led, home based self help treatment for patients in primary care with chronic fatigue syndrome: randomised controlled trial. *BMJ, 340*. doi: 10.1136/bmj.c1777

Wearden, A. J., Dunn, G., Dowrick, C., & Morriss, R. K. (2012). Depressive symptoms and pragmatic rehabilitation for chronic fatigue syndrome. *Br J Psychiatry, 201*(3), 227-232. doi: 10.1192/bjp.bp.111.107474

*Wearden, A. J., & Emsley, R. (2013). Mediators of the Effects on Fatigue of Pragmatic Rehabilitation for Chronic Fatigue Syndrome. *J Consult Clin Psychol*. doi: 10.1037/a0033561

*White, P., Sharpe, M., Chalder, T., DeCesare, J., & Walyin, R. (2007). Protocol for the PACE trial: a randomised controlled trial of adaptative pacing, cognitive behaviour therapy and graded exercise as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy. *BMC Neurol, 7*, 6. doi:10.1186/1471-2377-7-6

*White, P. D., Goldsmith, K. A., Johnson, A. L., Potts, L., Walwyn, R., DeCesare, J. C., . . . Sharpe, M. (2011). Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *The Lancet, 377*(9768), 823-836. doi:10.1016/S0140-6736(11)60096-2

*Wiborg, J. F., Knoop, H., Stulemeijer, M., Prins, J. B., & Bleijenberg, G. (2010). How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. *Psychological Medicine, 40*(08), 1281-1287doi: 10.1017/S0033291709992212

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatr Scand, 67*(6), 361-370.

Figure 1 Flowchart of studies

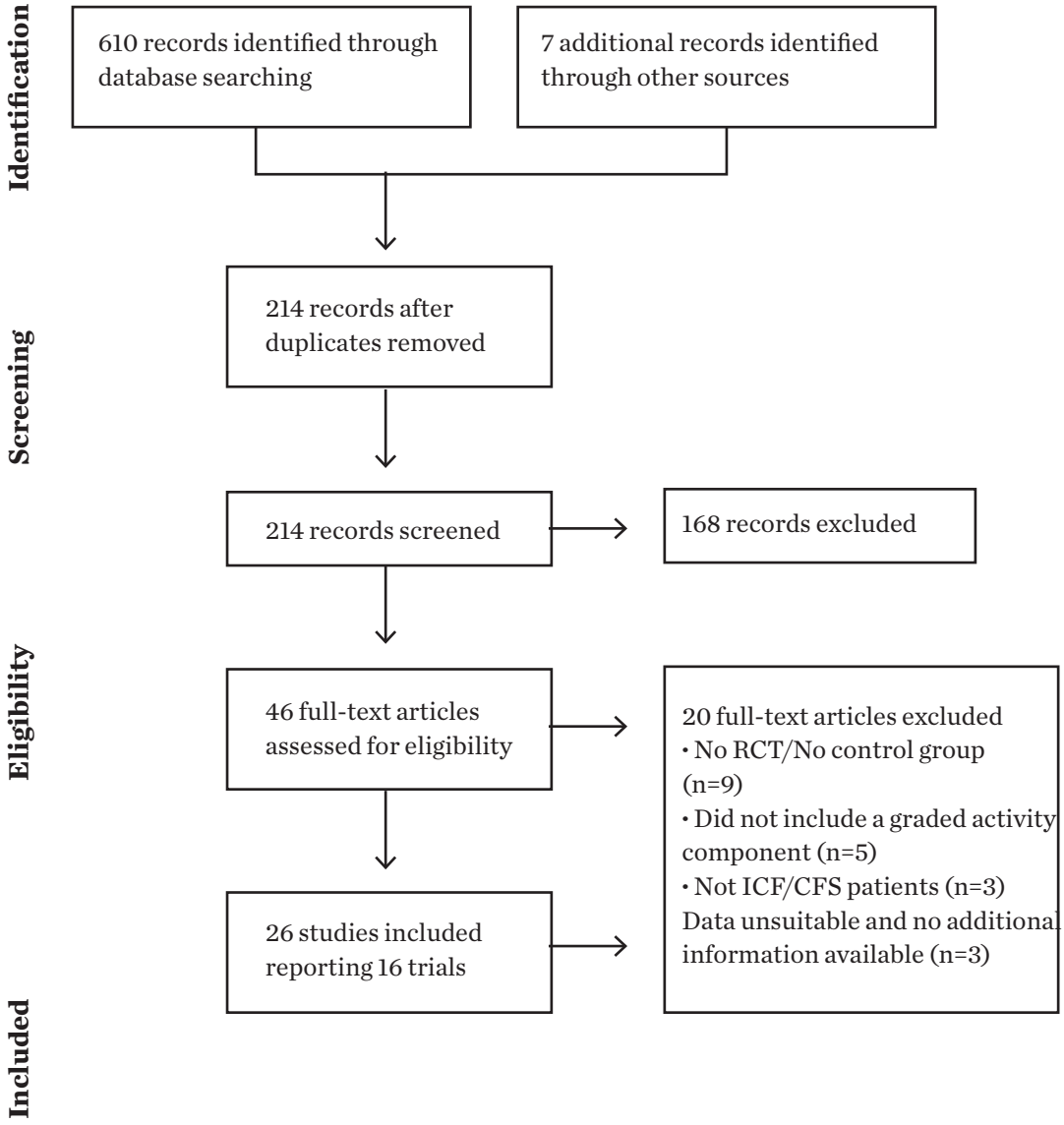


Table 1 Details of included studies

[a]First author, Year, Country	Population[b] / diagnostic criteria	[c]Sample size/ % women/ Age (mean)	[d]Drop out (%)	Setting	Provider	[e]Intervention condition	Control condition	Number and format of sessions/ length (weeks)	[f]Assessment points (months)	[g]Outcomes
Fulcher, 1997 UK	CFS / Oxford	66/ 74%/ 37	12	Secondary – tertiary care	Exercise physiologist	GET	Flexibility+ Relaxation**	12 face to face sessions /12 weeks	PT= 3	FAT, PF, PA, DEP
Wearden, 1998 UK	CFS/ Oxford	68/ 70%/ 39	32	Secondary – tertiary care	Physical therapist	GET+ drug placebo	Exercise placebo + drug placebo**	8 face to face sessions / 26 weeks	PT= 6.5	FAT, PA, DEP, ANX
Wallman, 2004, 2005 AU	CFS/ CDC	61/ 76.5%/ 45	0	University setting	Exercise physiologist	GET	Flexibiliy + relaxation**	1 face to face + 6 telephone calls/ 12 weeks	PT= 3-4	FAT, PA, DEP, ANX
Moss-Morris, 2005, NZ	CFS/ CDC	49/ 71%/ 41	12	Secondary – tertiary care	Psychologist	GET	Treatment as usual*	12 face to face sessions/12 weeks	PT=3	FAT, PF, PA
White, 2007, 2011, UK	CFS/ Oxford + severity	320/ 76.5% / 38	10	Secondary – tertiary care	Physical therapist, Exercise physiologist	GET	Treatment as usual*	14 face to face sessions 23 weeks	PT=6 FU=13	FAT, PF, PA, DEP, ANX
Ridsdale , 2012 UK	CFS/ CF>3M	146/ 79%/ 40	27	Primary care	Physical therapist	GET	Treatment as usual*	8 face to face sessions+ 2 tel. calls/24 weeks	PT=6 FU=12	FAT, PF, DEP, ANX
Powell, 2001, 2004, Bentall, 2002, UK	CFS/Oxford + severity	71/ 73%/ 34	13	Secondary – tertiary care	Psychologist	Pragmatic rehabilitation	Treatment as usual*	2 face to face sessions+2 telephone calls/12 weeks	PT=3 FU=12	FAT, PF, DEP, ANX
Wearden, 2006, 2010, 2013, UK	CFS/Oxford + severity	195/ 77%/ 44	15	Primary care (home visits)	Nurse	Pragmatic rehabilitation	Treatment as usual*	5 home visits+ 5 telephone calls/ 18 weeks	PT= 5 FU= 17	FAT, PF, PA, DEP, ANX

*[a]AU= Australia; NL= The Netherlands; NZ= New Zealand; UK= United Kingdom; US= United States of America. [b]CF= Chronic Fatigue; CFS= Chronic Fatigue Syndrome; ICF= Idiopathic Chronic Fatigue. [c]Sample characteristics at baseline. [d]Percentage of withdrawal in intervention condition. [e]GET=Graded Exercise Therapy; CBT= Cognitive-behavioral therapy. [f]Measurement periods included in the meta-analyses (months from baseline): PT= Post-treatment; FU= Follow-up.[g]FAT= Fatigue severity; PA= Physical activity; PF= Physical functioning; DEP= Depression; ANX= Anxiety. * Passive control group; **Active control group*

Table 1 Details of included studies (continued)

[a]First author, Year, Country	Population[b] / diagnostic criteria	[c]Sample size/ % women/ Age (mean)	[d]Drop out (%)	Setting	Provider	[e]Intervention condition	Control condition	Number and format of sessions/ length (weeks)	[f]Assessment points (months)	[g]Outcomes
Sharpe, 1996 ,UK	CFS/ Oxford + severity	60/68.5%/ 36	0	Secondary-tertiary care	Psychologist	CBT with graded exercise	Treatment as usual*	16 face to face sessions/ 16 weeks	PT=5 FU=12	FAT, PA, DEP, ANX
Deale, 1997, 2001, UK	CFS/CDC and oxford	60/68.5%/34.5	10	Secondary – tertiary care	Psychologist	CBT with graded exercise	Active relaxation**	13 face to face sessions /16-24 weeks	PT=6 FU=12	FAT, PF, DEP
Prins, 2001 Wiborg, 20 NL	ICF/CDC + severity	180/70.5%/ 36.5	35	Secondary – tertiary care	Pscyhotherapist	CBT with graded exercise	Treatment as usual*	16 face to face sessions /32 weeks	PT=8 FU=14	FAT, PF, PA
O'Dowd, 2006 ,UK	CFS/CDC	103/62.5%/ 44.5	17	Primary care	Psychologist Physical & occupat therapist	CBT with graded exercise	Treatment as usual*	8 face to face group sessions/16 weeks	PT=6 FU=12	FAT, PF, PA, DEP, ANX
Jason 2007, USA	CFS/CDC	57/83.3%/44	20	n/a	Nurse	CBT with graded exercise	Active relaxation**	13 face to face sessions/26 weeks	FU=12	FAT, PF, PA, DEP, ANX
Knoop, 2008 Tummers, 2010, 2013, Wiborg, 2010, NL	CFS CDC+ severity	169/79%/ 38	0.07	Secondary – tertiary care	Physical therapist	CBT with graded exercise	Waiting list*	1 face to face session + email or telephone calls every 2 weeks/≥16 weeks	PT=6	FAT, PF, PA
Tummers, 2012, 2013 NL	CFS CDC + severity	123/78%/36	11	Secondary – tertiary care	Nurse	CBT with graded exercise	Waiting list*	1 face to face session+ email every 2 weeks /≥20 weeks	PT=6	FAT, PF
Nunez, 2011, Spain	CFS/CDC	115/89.4 %/44	0.05	Secondary – tertiary care	Psychologist Physical therapist	Multiconvergent therapy + medication	Exercise counselling + medication**	9 face to face group session+36 group sessions/24 weeks	FU=12	PF

*[a]AU= Australia; NL= The Netherlands; NZ= New Zealand; UK= United Kingdom; US= United States of America. [b]CF= Chronic Fatigue; CFS= Chronic Fatigue Syndrome; ICF= Idiopathic Chronic Fatigue. [c]Sample characteristics at baseline. [d]Percentage of withdrawal in intervention condition. [e]GET=Graded Exercise Therapy; CBT= Cognitive-behavioral therapy.. [f]Measurement periods included in the meta-analyses (months from baseline): PT= Post-treatment; FU= Follow-up.[g]FAT= Fatigue severity; PA= Physical activity; PF= Physical functioning; DEP= Depression; ANX= Anxiety. * Passive control group; ** Active control group. n/a= information not available. n/a= information not available*

Table 2 Classification on Methodological quality, risk of bias and moderators of included interventions

Study ID	Total methodological quality[a]	Risk of bias				Psychological component	Minimal contact interventions[b]	Physical activity flexibility
		Allocation concealment	Assessor blinded	Inclusion drop-outs	Dropout information			
Fulcher	38	Low	Low	Low	Low	No	No	No
Wearden (1998)	42	Low	Low	Low	Low	No	No	No
Wallman	32	Unclear	Unclear	Low	Low	No	Yes *	Yes
Moss-Morris	33	Low	Unclear	Low	Low	No	No	No
White	51	Low	High	Low	Low	No	No	No
Ridsdale	41	Low	Unclear	Low	Low	No	No	No
Powell	41	Low	Unclear	Low	Low	Yes	Yes	Yes
Wearden (2010)	49	Low	Low	Low	Low	Yes	No **	Yes
Sharpe	42	Low	Unclear	Low	Low	Yes	No	No
Deale	42	Low	Unclear	Low	Low	Yes	No	No
Prins	44	Low	Unclear	Low	Low	Yes	No	Yes
O'Dowd	46	Low	Low	Low	Low	Yes	No	Yes
Jason	30	Unclear	Unclear	Unclear	High	Yes	No	No
Knoop	35	Low	Unclear	Low	Low	Yes	Yes	Yes
Tummers	40	Low	High	Low	Low	Yes	Yes	Yes
Nunez	29	Unclear	Unclear	High	Unclear	Yes	No	No

*[a] Range 0-58. [b] in contrast to more intensive interventions. *Did not provide a patient (self-help) manual. * Provided a patient (self-help) manual and direct-contact was provided through home visits.*

Table 3 Effects of interventions for each outcome at post-treatment and follow-up

Outcomes	**Assessment point**	**Sample size**	**Hedges' *g* (95% CI)**	***Z***	**Q**	***I²***	**No. of trials**
Fatigue	Post-treatment	1640	0.62 (0.45-0.79)	7.12**	34.84**	63%	14
	Follow-up	1164	0.67 (0.37-0.96)	4.51**	43.52**	82%	9
Physical functioning	Post-treatment	1451	0.30 (0.14-0.46)	3.59**	22.67*	56%	11
	Follow-up	1055	0.39 (0.13-0.66)	2.87**	30.45**	77%	8
Physical activity	Post-treatment	513	0.11 (-0.07-0.28)	1.21	4.64	35%	4
	Follow-up	634	0.41 (0.25-0.57)	5.01**	4.52	11%	5
[a]Physical capacity	Post-treatment	214	0.27 (0.00-0.54)	1.96*	10.90**	73%	4
Depression	Post-treatment	921	0.41 (0.22-0.59)	4.38**	16.56[†]	46%	10
	Follow-up	838	0.36 (0.14-0.58)	3.24**	13.17*	54%	7
Anxiety	Post-treatment	686	0.28 (0.13-0.43)	3.67**	2.70	0%	7
	Follow-up	778	0.22 (0.08-0.37)	3.13**	2.29	0%	6

*[†]p<0.10, *p<0.05; **p<0.01; [a]Data available only at post-treatment.*

Table 4 Subgroup analysis assessing the effect of study characteristics upon effect size at the longest assessment period available, separated by outcome

Moderator		Fatigue					Physical functioning					Physical activity	
		k	*g* (95% CI)	*Z*	*p*[1]	*I*[2]	*k*	*g* (95% CI)	*Z*	*p*[1]	*I*[2]	*k*	*g* (95% CI
Control condition	Passive	10	0.63 (0.27.99)	5.70**	0.81	80	9	0.33 (0.16-0.62)	2.46**	0.65	8	6	0.22 (-0.03-0.48)
	Active	5	0.68 (0.45-0.92)	3.40**		0	4	0.42 (0.10-0.81)	3.27**		84	4	0.37 (0.12-0.62)
[a]Setting	Primary	3	0.26 (-0.08-0.59)	1.44	0.01	0	3	0.15 (-0.17-0.47)	0.92	0.13	0	2	0.41 (-0.12-0.94)
	Secondary-tertiary	10	0.82 (0.59-0.96)	7.65**		69	9	0.44 (0.25-0.64)	4.42**		63	7	0.22 (-0.06-0.50)
[b]Provider	Nurse	3	0.53 (0.16-0.90)	2.73**	0.02	45	3	0.30 (-0.04-0.64)	1.71	0.18	0	2	0.13 (-0.31-0.53)
	Physical therapist Physiologist	5	0.43 (0.14-0.72)	2.90**		16	3	0.40 (0.07-0.73)	2.35*		63	4	0.44 (0.16-0.73)
	Psychologist, Psychotherapist	6	1.00 (0.72-1.28)	6.95**		72	5	0.69 (0.41-0.98)	4.74**		67	4	0.06 (-0.23-0.35)
Psychological component	No	6	0.50 (0-19-0.80)	3.25**	0.18	35	4	0.34 (0.02-0.73)	2.10*	0.89	22	5	0.28 (-0.04-0.60)
	Yes	9	0.77 (0.53-1.01)	6.31**		75	9	0.36 (0.19-0.66)	3.41**		66	6	0.27 (-0.01-0.55)
Flexibility in activity	No	8	0.59 (0.32-0.87)	3.43**	0.55	53	7	0.35 (0.11-0.65)	2.85**	0.90	75	6	0.31 (0.01-0.60)
	Yes	7	0.74 (0.46-1.02)	4.99**		81	6	0.36 (0.17-0.70)	3.90**		52	5	0.24 (-0.06-0.54)
Minimal contact	No	11	0.55 (0.34-0.75)	5.21**	0.04	37	10	0.32 (0.12-0.51)	3.22**	0.44	70	9	0.29 (0.06-0.53)
	Yes	4	0.96 (0.62-1.31)	5.48**		84	3	0.47 (0.13-0.82)	2.69**		50	2	0.20 (-0.27-0.69)
Meta-Regressions		***k***	**Slope**	***Z***	***p***		***k***	**slope**	***Z***	***p***		***k***	**slope**
Length of treatment		15	-0.03	-1.58	0.11		13	-0.02	1.29	0.24		11	-0.00
Methodological quality		15	-0.02	-0.91	0.36		13	0.01	0.93	0.35		11	0.02

*†p<0.10; *p<0.05; **p<0.01; [1]p-values correspond to subgroup differences in effects. a Wallman et al. (2004) trial was not included as it was the only study conducted in an university laboratory department; Jason et al (2007) study was not included as no information regarding the exact location setting was provided. bThe study conducted by O'Dowd (2006) was not included because the intervention was provided by specialists from multiple fields. n/a=not enough interventions in the subgroup to allow for a comparison*

Table 4 Subgroup analysis assessing the effect of study characteristics upon effect size at the longest assessment period available, separated by outcome (cont.)

Moderator		Physical activity			Depression				
		Z	*p*[1]	I^2	*k*	*g* (95% CI)	*Z*	*p*[1]	I^2
Control condition	Passive	1.70†	0.52	76	7	0.44 (0.21-0.66)	3.72**	0.26	73
	Active	1.97*		0	5	0.21 (0.10-0.53)	1.33		0
[a]Setting	Primary	1.52	n/a	75	3	0.15 (-0.18-0.48)	0.90	0.13	
	Secondary-tertiary	1.50		72	7	0.47 (0.23-0.71)	3.82**		70
[b]Provider	Nurse	0.57	n/a	0	2	0.35 (0.00-0.70)	1.99*	0.14	75
	Physical therapist Physiologist	3.23**		0	5	0.23 (-0.05-0.50)	1.63		0
	Psychologist, Psychotherapist	0.39		77	3	0.71 (0.32-1.11)	3.53**		67
Psychological component	No	1.70†	0.97	67	5	0.25 (-0.05-0.51)	3.15*	0.21	0
	Yes	1.90†		57	7	0.46 (0.16-0.76)	3.03**		71
Flexibility in activity	No	2.04	0.76	65	7	0.22 (-0.01-0.45)	1.86	0.09	0
	Yes	1.59		61	5	0.53 (0.26-0.80)	3.85**		78
Minimal contact	No	2.44*	n/a	64	9	0.22 (0.10-0.34)	3.50**	0.00	0
	Yes	0.84		56	3	0.85 (0.59-1.10)	6.52**		34
Meta-Regressions		***Z***	***P***		***k***	**Slope**	***Z***	***P***	
Length of treatment		-0.28	0.79		12	-0.03	-1.67	010	
Methodological quality		1.31	0.19		12	-0.01	-0.58	0.57	

*†p<0.10; *p<0.05; **p<0.01; [1]p-values correspond to subgroup differences in effects. a Wallman et al. (2004) trial was not included as it was the only study conducted in an university laboratory department; Jason et al (2007) study was not included as no information regarding the exact location setting was provided. bThe study conducted by O'Dowd (2006) was not included because the intervention was provided by specialists from multiple fields. n/a=not enough interventions in the subgroup to allow for a comparison*

Appendix A

Systematic Reviews Included in Reference List Search

Castell, B.D., Kazantsis, N. & Moss.Morris, R.E. (2011). Cognitive Behavioral Therapy and Graded Exercise for Chronic Fatigue Syndrome: A Meta Analysis. *Clinical Psychology Science and Practice, 18*(4), 311.

Chambers, D., Bagnall, A.M., Hempel, S. & Forbes, C. (2006). Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis: an updated systematic review. *Journal of the Royal Society of Medicine, 99*(10), 506-20.

Cho, H.J, Hotopf, M. & Wessely, S. (2005). The placebo response in the treatment of chronic fatigue syndrome: a systematic review and meta-analysis. Psychosomatic Medicine, 67(2), 301-13.

Edmonds, L., McGuire, L., & Price, J. (2004). Exercise Therapy for Chronic Fatigue Syndrome. *Cochrane Database Syst Rev, 3*, CD003200.

Malouff, J. M., Thorsteinsson, E. B., Rooke, S. E., Bhullar, N., & Schutte, N. S. (2008). Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: A meta analysis. *Clinical Psychology Review, 28*(5), 736.

Price, J., Mitchell, E., Tidy, E., & Hunot, V. (2008). Cognitive behaviour therapy for chronic fatigue syndrome in adults. *Cochrane Database Syst Rev, 3*, CD001027.

Appendix B

Table B.1 Full-Text Studies Excluded and Reasons for Exclusion

Study author(s), year of publication & publication title	Reason for exclusion
Black, C.D., O'Connor, P.J. & McCully, K. (2005). Increased Daily physical activity and fatigue symptoms in chronic fatigue syndrome. *Dynamic Medicine*, 4:3.	Healthy controls (not ICF/CFS patients)
Burgess, M., Chalder,T. & Andiappan, M. (2012). Cognitive Behaviour Therapy for Chronic Fatigue Syndrome in Adults: Face-to-Face versus Telephone Treatment: A Randomized Controlled Trial. *Psychological Medicine*, 40(2): 175-91.	No control group
Chalder, T., Wallace, P. & Wessely, S. (1997). Self-help treatment of chronic fatigue in the community: A randomized controlled trial. British *Journal of Health Psychology*, *2*, 189-197.	Did not include a graded activity component
Cox, D.L. (2002). Chronic Fatigue Syndrome: An evaluation of an occupational therapy inpatient intervention. *British Journal of Occupational Therapy, 65,* 461-68.	No RCT
Friedberg, F. & Krupp, L.B. (1994). A comparison of cognitive behavioral treatment for chronic fatigue syndrome and primary depression. *Clinical Infectious Diseases,* 18 (Supp 1), S105-10.	No RCT Did not include a graded activity component
Friedberg, F., Napoli, A., Coronel, J., Adamowicz, J., Seva, V., Caikauskaite, I.,...Meng, H. (2013). Chronic fatigue self-management in primary care: A randomized trial. *Psychosomatic Medicine,* 75: 650-57. doi: 10.1097/PSY.0b013e31829dbed4	Did not include a graded activity component
Goudsmit, E.M., Ho-Yen, D.O. & Dancey, C.P. (2009). Learning to cope with chronic illness: Efficacy of a multi-component treatment for people with chronic fatigue syndrome. *Patient Education and Counselling, 77,* 231-236.	No RCT Did not include a graded activity component

ICF= Idiopathic Chronic Fatigue; CFS = Chronic Fatigue Syndrome; RCT= Randomized Controlled Trial

Table B.1 Full-Text Studies Excluded and Reasons for Exclusion (cont.)

Study author(s), year of publication & publication title	Reason for exclusion
Huibers, M.J. et al (2004). Efficacy of a cognitive-behavioural therapy by general practitioners for unexplained fatigue among employees: Randomised controlled trial. *British Journal of Psychiatry, 184*, 240-246.	Did not include a graded activity component Not ICF/CFS patients.
Lloyd, A. et al. (1993). Immunological and psychological therapy for patients with chronic fatigue syndrome: a double-blind, placebo-controlled trial. *American Journal of Medicine, 94,* 97.	Statistical data unsuitable
Lopez. C. et al (2011). A pilot study of cognitive behavioural stress management effects on stress, quality of life, and symptoms in persons with chronic fatigue syndrome. *Journal of Psychosomatic Research, 70*, 328.	Did not include a graded activity component.
Marlin, R.G. et al. (1998). An Evaluation of Multidisciplinary Intervention for Chronic Fatigue Syndrome with Long-Term Follow-Up, and a Comparison with Untreated Controls. *The American Journal of Medicine, 105*(3A), 110S.	Statistical data unsuitable
Poppe, C, Petrovic, M., Vogelaers, D. & Crombez, G. (2013). Cognitive behavior therapy in patients with chronic fatigue syndrome: The role of illness acceptance and neuroticism. *Journal of Psychosomatic Research*, *74,* 367-372.1085-1094.	No RCT
Quarmby, L., Rimes, K.A., Deale, A., Wessely, S. & Chalder, T. (2007). Cognitive-behaviour therapy for chronic fatigue syndrome: Comparison of outcomes within and outside the confines of a randomised controlled trial. Behaviour Research and Therapy, 45,	No RCT
Ridsdale, L. et al. (2001). Chronic Fatigue in general practice: Is counselling as good as cognitive behaviour therapy? A UK randomized trial. *British Journal of General Practice*, *51*, 19-24.	No control group

ICF= Idiopathic Chronic Fatigue; CFS = Chronic Fatigue Syndrome; RCT= Randomized Controlled Trial

Table B.1 Full-Text Studies Excluded and Reasons for Exclusion

Study author(s), year of publication & publication title	**Reason for exclusion**
Ridsdale, L., Darbshire, L. & Seed, P.Y. (2004). Is graded exercise better than cognitive behaviour therapy for fatigue? A UK randomised trial in primary care. *Psychological Medicine, 34,* 37-49.	No control group
Saxty M & Hansen Z. (2005). Group Cognitive Behavioral Therapy for Chronic Fatigue Syndrome: A Pilot Study. *Behavioural and Cognitive Psychology, 33*,311-318.	Not RCT
Söderberg, S. & Evengård, B. (2001). Short-term group therapy for patients with Chronic Fatigue Syndrome. *Psychotherapy and Psychosomatics, 70*(2),108-111.	Did not include a graded activity component
Stubhaug, B., Lie, S. A., Ursin, H. & Eriksen, H.R. (2008). Cognitive-behavioral therapy v. mirtazapine for chronic fatigue and neuroasthenia: randomized placebo-controlled trial. *British Journal of Psychiatry, 192,* 217-223.	Not ICF/CFS
Thomas, M.A. et al. (2008). A multiconvergent to the rehabilitation of patients with chronic fatigue syndrome: a comparative study. *Physiotherapy, 94,* 35-42.	Statistical data unsuitable
Whitehead L. & Champion, P. (2002). Can general practitioners manage chronic fatigue syndrome? A controlled trial. *Journal of Chronic Fatigue Syndrome, 10,* 55-64.	Statistical data unsuitable

ICF= Idiopathic Chronic Fatigue; CFS = Chronic Fatigue Syndrome; RCT= Randomized Controlled Trial

Appendix C

Table C.1 Consensus Ratings of Methodological Quality

	Included studies															
Methodological Criterion	Fulcher	Wearden (1998)	Wallman	Moss-Morris	White	Ridsdale	Powell	Wearden (2010)	Sharpe	Deale	Prins	O'Dowd	Jason	Knoop	Tummers	Nunez
1-Clear objectives	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
2-Sample size	1	1	1	1	2	2	1	2	2	1	2	2	1	2	2	1
3-Trial duration	2	2	1	1	2	2	2	2	2	2	2	2	2	1	1	2
4-Power calculation	2	2	2	2	2	2	2	2	2	2	2	2	0	2	2	1
5-Allocation method	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1
6-Allocation concealment	2	2	1	2	2	2	2	2	2	2	1	2	0	2	2	0
7-Treatment clearly described	2	2	2	2	2	2	2	2	1	2	2	2	2	1	2	2
8-Manualized treatment	0	0	0	0	2	1	0	2	2	1	1	2	1	1	1	1
9-Representative sample	2	2	1	1	2	2	2	2	2	2	2	2	1	1	2	1
10-Inclusion criteria	1	1	1	1	2	1	2	2	2	1	2	1	1	2	2	1
11-Exclusion criteria	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
12-Described demographics	0	1	0	1	2	2	2	2	2	2	2	2	2	1	1	1
13-Assessor blinded	1	1	0	0	0	0	0	2	0	1	0	1	0	0	0	0
14-Treatment compliance	1	2	1	1	2	1	1	1	1	0	1	1	1	1	1	0
15-Treatment side effects	1	0	0	0	2	0	0	1	1	0	0	1	0	0	0	0
16-Dropout information	2	2	2	2	1	1	1	2	1	2	1	2	0	1	2	1
17-Outcome measures	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
18-Between-group comparisons	2	2	1	1	2	2	1	2	1	2	2	2	1	2	2	1
19-Dropout inclusion	1	2	2	1	2	2	1	1	1	1	2	2	0	2	2	0
20-Well-presented results	2	1	2	2	2	2	2	2	1	2	2	1	1	1	2	1
21-Appropriate analysis	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	1
22-Justified conclusions	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
23-Insterests declared	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
24-Allegance to therapy	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
25-Follow-up duration	1	0	0	0	1	1	2	2	1	1	1	1	1	0	0	1
26-Cointervention avoided	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1
27-Drug use assessed	1	2	0	0	2	0	1	2	1	1	0	2	0	0	0	1
28-Tratment credibility	0	0	0	0	2	1	0	1	0	0	1	1	1	0	1	0
29-Consecutive subjects	0	2	0	0	2	0	2	0	2	2	2	0	0	0	0	1
Total Quality	38	42	32	33	51	41	41	49	42	42	44	46	30	35	40	29

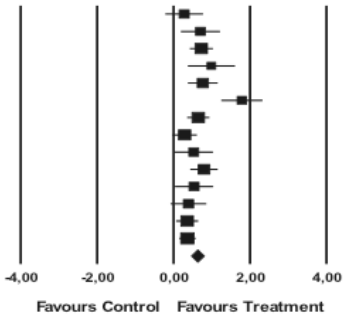
0 = Not done and/or not reported; 1= Done and/or reported to some extent; 2 = Adequately done and/or adequately reported

Appendix D

Forest plots for all outcomes at post-treatment, follow-up and longest period of assessment

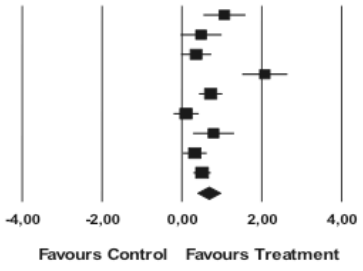
Effect sizes for fatigue severity at posttreatment

Study name	Outcome	Time point	Hedges's g	Lower limit	Upper limit	p-Value
Deale, 1997	Fatigue severity	posttreatment	0,277	-0,225	0,779	0,279
Fulcher, 1997	Fatigue severity	posttreatment	0,703	0,184	1,222	0,008
Knoop, 2008	Fatigue severity	posttreatment	0,727	0,417	1,037	0,000
Moss-Morris, 2001	Fatigue severity	posttreatment	0,990	0,367	1,613	0,002
O Dowd, 2006	Fatigue severity	posttreatment	0,766	0,368	1,163	0,000
Powell, 2001	Fatigue severity	posttreatment	1,787	1,240	2,333	0,000
Prins,2001	Fatigue severity	posttreatment	0,645	0,346	0,944	0,000
Ridsdale 2012	Fatigue severity	posttreatment	0,292	-0,033	0,616	0,078
Sharpe, 1996	Fatigue severity	posttreatment	0,529	0,021	1,037	0,041
Tummers, 2012	Fatigue severity	posttreatment	0,796	0,431	1,162	0,000
Wallman, 2004	Fatigue severity	posttreatment	0,535	0,030	1,041	0,038
Wearden, 1998	Fatigue severity	posttreatment	0,389	-0,085	0,864	0,108
Wearden, 2010	Fatigue severity	posttreatment	0,356	0,060	0,652	0,018
White, 2011	Fatigue severity	posttreatment	0,362	0,141	0,582	0,001
			0,618	0,448	0,788	0,000



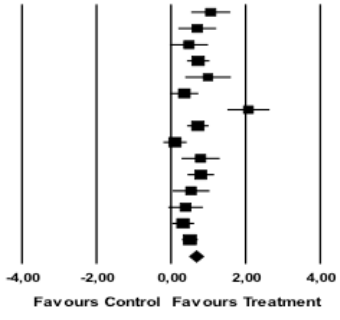
Effect sizes for fatigue severity at follow-up

Study name	Outcome	Time point	Hedges's g	Lower limit	Upper limit	p-Value
Deale, 1997	Fatigue severity	follow-up	1,064	0,530	1,599	0,000
Jason, 2007	Fatigue severity	follow-up	0,479	-0,040	0,999	0,071
O Dowd, 2006	Fatigue severity	follow-up	0,355	-0,032	0,741	0,072
Powell, 2001	Fatigue severity	follow-up	2,075	1,502	2,648	0,000
Prins,2001	Fatigue severity	follow-up	0,720	0,419	1,020	0,000
Ridsdale 2012	Fatigue severity	follow-up	0,104	-0,220	0,427	0,530
Sharpe, 1996	Fatigue severity	follow-up	0,791	0,272	1,310	0,003
Wearden, 2010	Fatigue severity	follow-up	0,321	0,017	0,626	0,038
White, 2011	Fatigue severity	follow-up	0,505	0,283	0,727	0,000
			0,666	0,377	0,956	0,000



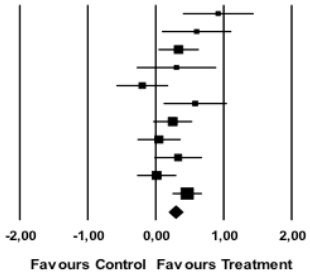
Effect sizes for fatigue severity at longest period of assessment

Study name	Outcome	Time point	Hedges's g	Lower limit	Upper limit	p-Value
Deale, 1997	Fatigue severity	follow-up	1,064	0,530	1,599	0,000
Fulcher, 1997	Fatigue severity	posttreatment	0,703	0,184	1,222	0,008
Jason, 2007	Fatigue severity	follow-up	0,479	-0,040	0,999	0,071
Knoop, 2008	Fatigue severity	posttreatment	0,727	0,417	1,037	0,000
Moss-Morris, 2001	Fatigue severity	posttreatment	0,990	0,367	1,613	0,002
O Dowd, 2006	Fatigue severity	follow-up	0,355	-0,032	0,741	0,072
Powell, 2001	Fatigue severity	follow-up	2,075	1,502	2,648	0,000
Prins,2001	Fatigue severity	follow-up	0,720	0,419	1,020	0,000
Ridsdale 2012	Fatigue severity	follow-up	0,104	-0,220	0,427	0,530
Sharpe,1996	Fatigue severity	follow-up	0,791	0,272	1,310	0,003
Tummers, 2012	Fatigue severity	posttreatment	0,796	0,431	1,162	0,000
Wallman, 2004	Fatigue severity	posttreatment	0,535	0,030	1,041	0,038
Wearden, 1998	Fatigue severity	posttreatment	0,389	-0,085	0,864	0,108
Wearden, 2010	Fatigue severity	follow-up	0,321	0,017	0,626	0,038
White, 2011	Fatigue severity	follow-up	0,505	0,283	0,727	0,000
			0,663	0,472	0,854	0,000



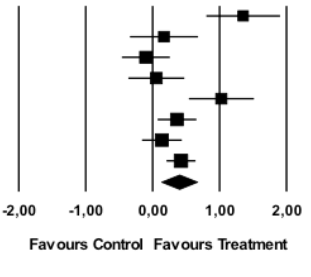
Effect sizes for functioning at posttreatment

Study name	Outcome	Time point	Hedges's g	Lower limit	Upper limit	p-Value
Deale, 1997	Functioning	posttreatment	0,919	0,393	1,445	0,001
Fulcher, 1007	Functioning	posttreatment	0,602	0,087	1,117	0,022
Knoop, 2008	Functioning	posttreatment	0,336	0,034	0,638	0,029
Moss-Morris, 2001	Functioning	posttreatment	0,305	-0,285	0,896	0,311
O Dowd, 2006	Functioning	posttreatment	-0,198	-0,582	0,186	0,313
Powell, 2001	Functioning	posttreatment	0,580	0,110	1,051	0,016
Prins,2001	Functioning	posttreatment	0,250	-0,042	0,543	0,093
Ridsdale 2012	Functioning	posttreatment	0,049	-0,274	0,372	0,767
Tummers, 2012	Functioning	posttreatment	0,330	-0,023	0,684	0,067
Wearden, 2010	Functioning	posttreatment	0,014	-0,279	0,308	0,925
White, 2011	Functioning	posttreatment	0,463	0,242	0,685	0,000
			0,289	0,186	0,392	0,000



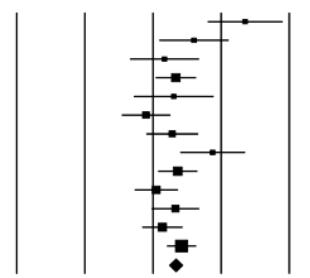
Effect sizes for functioning at follow-up

Study name	Outcome	Time point	Hedges's g	Lower limit	Upper limit	p-Value
Deale, 1997	Functioning	follow-up	1,353	0,798	1,908	0,000
Jason, 2007	Functioning	follow-up	0,170	-0,343	0,683	0,516
Nunez, 2011	Functioning	follow-up	-0,101	-0,465	0,262	0,585
O Dowd, 2006	Functioning	follow-up	0,056	-0,367	0,479	0,795
Powell, 2001	Functioning	follow-up	1,028	0,537	1,518	0,000
Prins,2001	Functioning	follow-up	0,364	0,070	0,657	0,015
Wearden, 2010	Functioning	follow-up	0,139	-0,164	0,441	0,369
White, 2011	Functioning	follow-up	0,424	0,203	0,645	0,000
			0,394	0,125	0,663	0,004



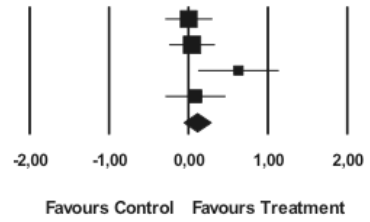
Effect sizes for functioning at longest period of assessment

Study name	Outcome	Time point	Hedges's g	Lower limit	Upper limit	p-Value
Deale, 1997	Functioning	follow-up	1,353	0,798	1,908	0,000
Fulcher, 1997	Functioning	postreatment	0,602	0,087	1,117	0,022
Jason, 2007	Functioning	follow-up	0,170	-0,343	0,683	0,516
Knoop, 2008	Functioning	posttreatment	0,336	0,034	0,638	0,029
Moss-Morris, 2001	Functioning	posttreatment	0,305	-0,285	0,896	0,311
Nunez, 2011	Functioning	follow-up	-0,101	-0,465	0,262	0,585
O Dowd, 2006	Functioning	follow-up	0,283	-0,103	0,668	0,150
Powell, 2001	Functioning	follow-up	0,876	0,394	1,359	0,000
Prins,2001	Functioning	follow-up	0,364	0,070	0,657	0,015
Ridsdale 2012	Functioning	posttreatment	0,049	-0,274	0,372	0,767
Tummers, 2012	Functioning	posttreatment	0,330	-0,023	0,684	0,057
Wearden, 2010	Functioning	follow-up	0,139	-0,164	0,441	0,369
White, 2011	Functioning	follow-up	0,420	0,199	0,641	0,000
			0,329	0,231	0,428	0,000



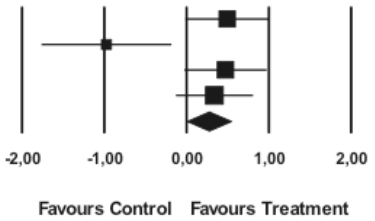
Effect sizes for physical activity at posttreatment

Study name	Outcome	Time point	Hedges's g	Lower limit	Upper limit	p-Value
Knoop, 2008	Activity	posttreatment	0,004	-0,296	0,305	0,977
Prins, 2001	Activity	posttreatment	0,045	-0,246	0,336	0,764
Sharpe, 1996	Activity	posttreatment	0,630	0,118	1,142	0,016
Wearden, 2010	Activity	posttreatment	0,088	-0,294	0,470	0,652
			0,107	-0,066	0,279	0,226



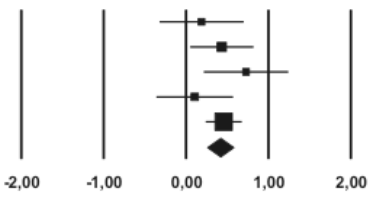
Effect sizes for physical capacity at posttreatment

Study name	Outcome	Time point	Hedges's g	Lower limit	Upper limit	p-Value
Fulcher, 1997	Activity	posttreatment	0,493	-0,018	1,005	0,059
Moss-Morris, 2001	Activity	posttreatment	-0,974	-1,766	-0,182	0,016
Wallman, 2004	Activity	posttreatment	0,473	-0,031	0,976	0,066
Wearden, 1998	Activity	posttreatment	0,339	-0,135	0,812	0,161
			0,268	-0,000	0,537	0,050



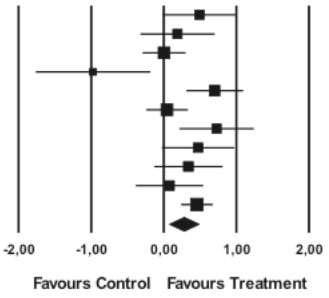
Effect sizes for physical activity at follow-up

Study name	Outcome	Time point	Hedges's g	Lower limit	Upper limit	p-Value
Jason, 2007	physical activity	follow-up	0,189	-0,324	0,702	0,471
O'Dowd, 2006	physical activity	pooled	0,434	0,046	0,822	0,028
Sharpe, 1996	physical activity	follow-up	0,729	0,213	1,245	0,006
Wearden, 2010	physical activity	follow-up	0,106	-0,363	0,574	0,658
White, 2011	physical activity	follow-up	0,457	0,236	0,678	0,000
			0,412	0,252	0,572	0,000



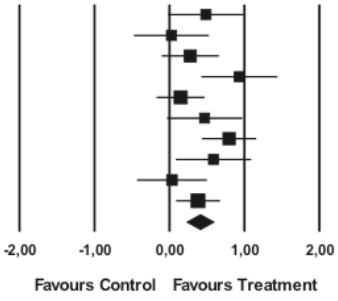
Effect sizes for physical activity/capacity at longest period of assessment

Study name	Outcome	Time point	Hedges's g	Lower limit	Upper limit	p-Value
Fulcher, 1997	activity_capacity	posttreatment	0,493	-0,018	1,005	0,059
Jason, 2007	activity_capacity	follow-up	0,189	-0,324	0,702	0,471
Knoop, 2008	activity_capacity	posttreatment	0,004	-0,296	0,305	0,977
Moss-Morris, 2005	activity_capacity	posttreatment	-0,974	-1,766	-0,182	0,016
O Dowd, 2006	activity_capacity	pooled	0,702	0,306	1,097	0,001
Prins, 2001	activity_capacity	posttreatment	0,045	-0,246	0,336	0,764
Sharpe,1996	activity_capacity	follow-up	0,729	0,213	1,245	0,006
Wallman, 2004	activity_capacity	posttreatment	0,473	-0,031	0,976	0,066
Wearden, 1998	activity_capacity	posttreatment	0,339	-0,135	0,812	0,161
Wearden, 2010	activity_capacity	follow-up	0,079	-0,390	0,547	0,742
White, 2011	activity_capacity	follow-up	0,457	0,236	0,678	0,000
			0,274	0,070	0,478	0,008



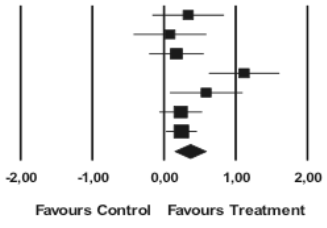
Effect sizes for depression at posttreatment

Study name	Outcome	Time point	Hedges's g	Lower limit	Upper limit	p-Value
Deale, 1997	depression	posttreatment	0,486	-0,021	0,993	0,060
Fulcher, 1997	depression	posttreatment	0,027	-0,477	0,530	0,917
O'Dowd, 2006	depression	posttreatment	0,278	-0,108	0,663	0,158
Powell, 2001	depression	posttreatment	0,932	0,421	1,442	0,000
Ridsdale 2012	depression	posttreatment	0,150	-0,174	0,473	0,364
Sharpe, 1996	depression	posttreatment	0,469	-0,038	0,975	0,070
Tummers, 2012	depression	posttreatment	0,796	0,431	1,162	0,000
Wallman, 2004	depression	posttreatment	0,587	0,080	1,094	0,023
Wearden, 1998	depression	posttreatment	0,034	-0,436	0,504	0,888
Wearden, 2010	depression	posttreatment	0,380	0,084	0,676	0,012
			0,405	0,224	0,586	0,000



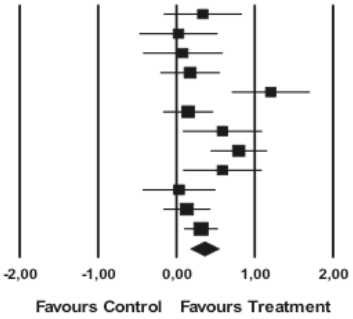
Effect sizes for depression at follow-up

Study name	Outcome	Time point	Hedges's g	Lower limit	Upper limit	p-Value
Deale, 1997	depression	follow-up	0,337	-0,166	0,840	0,190
Jason, 2007	depression	follow-up	0,083	-0,430	0,595	0,752
O Dowd, 2006	depression	follow-up	0,173	-0,211	0,557	0,378
Powell, 2001	depression	follow-up	1,117	0,621	1,613	0,000
Sharpe, 1996	depression	follow-up	0,588	0,077	1,098	0,024
Wearden, 2010	depression	follow-up	0,233	-0,070	0,536	0,133
White, 2011	depression	follow-up	0,242	0,023	0,461	0,031
			0,362	0,143	0,581	0,001



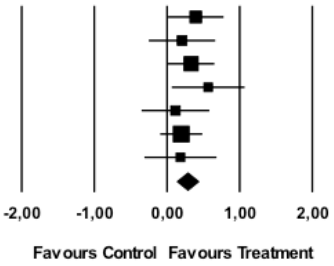
Effect sizes for depression at longest period of assessment

Outcome	Study name	Time point	Hedges's g	Lower limit	Upper limit	p-Value
depression	Deale, 1997	follow-up	0,337	-0,166	0,840	0,190
depression	Fulcher, 1997	posttreatment	0,027	-0,477	0,530	0,917
depression	Jason, 2007	follow-up	0,083	-0,430	0,595	0,752
depression	O Dowd, 2006	follow-up	0,175	-0,209	0,559	0,371
depression	Powell, 2001	follow-up	1,204	0,703	1,705	0,000
depression	Ridsdale 2012	posttreatment	0,150	-0,174	0,473	0,364
depression	Sharpe, 1996	follow-up	0,588	0,077	1,098	0,024
depression	Tummers, 2012	posttreatment	0,796	0,431	1,162	0,000
depression	Wallman, 2004	posttreatment	0,587	0,080	1,094	0,023
depression	Wearden, 1998	posttreatment	0,034	-0,436	0,504	0,888
depression	Wearden, 2010	follow-up	0,133	-0,169	0,436	0,387
depression	White, 2011	follow-up	0,315	0,095	0,535	0,005
			0,355	0,174	0,537	0,000



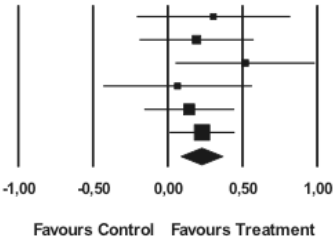
Effect sizes for anxiety at posttreatment

Study name	Outcome	Time point	Hedges's g	Lower limit	Upper limit	p-Value
O Dowd, 2006	anxiety	posttreatment	0,397	0,009	0,784	0,045
Powell, 2001	anxiety	posttreatment	0,207	-0,255	0,668	0,381
Ridsdale 2012	anxiety	posttreatment	0,333	0,008	0,658	0,045
Wallman, 2004	anxiety	posttreatment	0,568	0,061	1,074	0,028
Wearden, 1998	anxiety	posttreatment	0,116	-0,354	0,587	0,628
Wearden, 2010	anxiety	posttreatment	0,196	-0,098	0,491	0,191
Sharpe, 1996	anxiety	posttreatment	0,186	-0,315	0,686	0,468
			0,279	0,130	0,429	0,000



Effect sizes for anxiey at follow-up

Study name	Outcome	Time point	Hedges's g	Lower limit	Upper limit	p-Value
Jason, 2007	anxiety	follow-up	0,305	-0,210	0,821	0,245
O Dowd, 2006	anxiety	follow-up	0,192	-0,192	0,577	0,327
Powell, 2001	anxiety	follow-up	0,518	0,049	0,986	0,030
Sharpe, 1996	anxiety	follow-up	0,065	-0,434	0,565	0,797
Wearden, 2010	anxiety	follow-up	0,143	-0,159	0,446	0,353
White, 2011	anxiety	follow-up	0,229	0,010	0,448	0,041
			0,224	0,084	0,365	0,002



05

Protocol for the "four steps to control your fatigue (4-STEPS)" randomised controlled trial: A self-regulation based physical activity intervention for patients with unexplained chronic fatigue

Manuscript published
M. Marques, V. De Gucht, S. Maes & I. Leal (2012). Protocol for the "four steps to control your fatigue (4-steps)" randomised controlled trial: a self-regulation based physical activity intervention for patients with unexplained chronic fatigue. *BMC Public Health,* 12:202.

Abstract

Background: Unexplained Chronic Fatigue is a medical condition characterized by the presence of persistent, severe and debilitating medically unexplained fatigue, leading to impaired functioning and lower quality of life. Research suggests that physical activity can contribute to the reduction of fatigue and other somatic symptoms and can thus significantly improve physical functioning and quality of life in these patients. Based on the self-regulation (SR) theory of behaviour change, we developed a brief physical activity program for patients suffering from unexplained chronic fatigue which focuses on the training of self-regulation skills, the "4-STEPS to control your fatigue" program.
Methods/Design*:* This is a multi-centre, randomised controlled trial (RCT) that will be carried out in local primary care centres and at the Portuguese Fibromyalgia and Chronic Fatigue Syndrome Patients Association. Patients aged between 18 and 65 and fulfilling operationalized criteria for Idiopathic Chronic Fatigue (ICF) and Chronic Fatigue Syndrome (CFS) will be recruited and randomly allocated to standard care (SC) or standard care plus a self-regulation based physical activity program (4-STEPS). Patients will be assessed at baseline, after the intervention (3 months) and at 12 months follow-up. The primary outcome is fatigue severity.
Discussion: The results of the RCT will provide information about the effectiveness of a brief self-regulation intervention for promoting physical activity in patients with unexplained chronic fatigue. If the program proves to be effective, it may be considered as an adjunctive treatment for these patients.

Trial Registration: ISRCTN70763996

Keywords: Unexplained Chronic Fatigue, Physical activity, Self-Regulation, Randomized Controlled Trial

Background

Fatigue is a common symptom in adults worldwide, being reported by around 20% of patients seeking medical care [1]. A recent epidemiological review concluded that physical activity can reduce fatigue and improve energy [1]. Recent literature emphasizes that fatigue should be considered as a multidimensional concept, incorporating both physical and mental fatigue [2]. Due to its subjective nature, fatigue is difficult to define and measure. It is a personal experience that cannot be objectively measured [3].

In most cases, fatigue is transient, but for some, fatigue symptoms become chronic, resulting in disability [4]. When fatigue lasts for at least six months, is not alleviated by rest, is debilitating, results in a significant reduction of daily activities and cannot be explained by an organic disease (unexplained chronic fatigue), it is classified as Idiopathic Chronic Fatigue (ICF) [4,5]. If ICF is accompanied by four or more of the following symptoms - unrefreshing sleep, lengthy malaise after exertion (lasting for over 24 hours), impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain without swelling or redness and headaches of a new type or severity - it is diagnosed as Chronic Fatigue Syndrome (CFS) according to the Center for Disease Control (CDC) criteria [6].

CFS prevalence has been reported to be in between 0.2% and 2% in general population samples [7]. Prevalence rates vary according to several factors such as the criteria used to diagnose CFS [4]. In terms of prognosis, a systematic review conducted by Cairns and Hotpof [8] found that full recovery from untreated CFS is rare. It is more common for patients to experience an improvement in symptom severity. CFS etiology remains unknown [4] and it is considered to be associated with a combination of several predisposing (e.g. genes), precipitating (e.g. life events) and perpetuating (e.g. physical inactivity) factors [9].

Patients with unexplained chronic fatigue often report complaints related to exercise intolerance and post-exertional malaise [4]. Prins, van der Meer and Bleijenberg [9] considered patients' perceptions and expectations related to symptom exacerbation as a consequence of exercise, to be the main cause

of the reduced levels of physical activity found in patients with unexplained chronic fatigue, rather than physical fitness limitations per se. Other studies pointed out that lack of physical activity and excessive resting are factors that result in physical deconditioning which, in turn, perpetuates fatigue and physical disability [10]. It has therefore been recommended that ICF/CFS patients engage in physical activity instead of refraining from it to manage their symptoms [10,11,12].

To promote physical activity in ICF/CFS, Graded Exercise Therapy (GET) has been recommended. GET is based on the assumption that in patients with unexplained chronic fatigue, physical activity must be initiated at a level that doesn't exacerbate symptoms and must be gradually increased until patients reach an optimal level of activity. Graded exercise programs follow the exercise prescription guidelines from the American College of Sports Medicine [13], tailored to each patient's level of physical activity. GET is usually delivered by an exercise physiologist or physical therapist, and consists of supervised exercise sessions and/or home-based exercise prescription (e.g. walking). Research has demonstrated that GET has a positive effect on physical activity and leads to decreased levels of fatigue [14,15,16,17].

Cognitive-behavioral therapy (CBT) has also demonstrated to be an effective treatment approach to CF. CBT interventions developed for ICF/CFS patients focus primarily on changing illness cognitions and expectations, as well as increasing control over symptoms. The CBT model makes a distinction between precipitating factors - factors that contribute to the initiation of a health problem - and perpetuating factors - factors that contribute to the maintenance of the health problem [18]. Since physical inactivity is considered to be a perpetuating factor of unexplained chronic fatigue, most CBT interventions also focus on physical activity promotion. A recent review conducted by Price and colleagues [19] concluded that CBT interventions have a positive effect on fatigue, depression and anxiety in ICF/CFS patients.

In patients with unexplained chronic fatigue a "boom and bust pattern" is frequently found, that is, a systematic alternation between periods of excessive activity (when feeling good), and, as a consequence of that, feeling extremely fatigued and having to

rest for longer periods of time [20, 21]. Pacing, which is having an appropriate balance between activity and rest, is considered to be an important technique for reducing fatigue symptoms. Pacing implies that patients are encouraged to set realistic goals on a daily basis in terms of activity and rest periods; it is often combined with graded exercise [22, 23].

CBT uses several self-regulation (SR) techniques.

SR can be defined as a sequence of actions and/or steering processes intended to attain a personal goal [26]. According to SR theory, individuals set personally important goals that guide their behavior [27]. In this goal-guidance process, self-regulation cognitions (e.g. self-efficacy expectations and autonomous/controlled motivation), emotions (positive and negative affect) and skills (e.g. self-monitoring and feedback), are considered to play an important role, both in goal setting, active goal pursuit and goal maintenance/attainment [27]. As a consequence, SR models not only contribute to our understanding of the influence of life goals on medically unexplained physical symptoms (MUPS) in general, and fatigue in particular [24], but interventions based upon these models may also encourage patients to change their personal goals from symptom avoidance to more active and positive goals [25]. In their review, Maes & Karoly [27] distinguished a number of self-regulation strategies associated with behavior change and derived a set of guidelines for interventions. These self-regulation core processes are: realistic outcome expectations; illness representations; goal setting (personal goals, ownership); planning; progress evaluation and feedback; efficacy support; attention and emotion control; control over competing goals; self-monitoring; self-reinforcement; facilitate social support; goal reformulation; relapse prevention; anticipatory coping [27].

One of the main intervention techniques based on self-regulation theory is Motivational Interviewing (MI), developed by Miller & Rollnick [28]. MI is a directive, client-centered technique for eliciting behavior change, by helping clients to explore and resolve perceived conflicts (ambivalence) with respect to behavior change and analyze the discrepancies between their current behavior and their life goals and values. It aims at increasing autonomous regulation and self-efficacy (i.e. confidence in one's ability to

perform a certain behavior) and promotes the transition from planning (motivational phase) to action (goal pursuit). MI has been successful in promoting physical activity in healthy populations [29], but there is limited research on MI interventions in patients with ICF/CFS and other MUPS. Powell and colleagues [30] evaluated an intervention based upon MI techniques to encourage graded physical exercise in CFS patients. The intervention led to increased physical functioning and decreased fatigue. In addition, the minimum intervention condition, consisting of only two face-to-face sessions, proved to be as successful as more extended versions of the program. A study conducted with fibromyalgia patients also showed a significant increase in physical exercise frequency, as well as reduced pain and physical impairment after an MI intervention [31].

Based on the empirical literature we developed a brief self-regulation based physical activity program for patients suffering from unexplained chronic fatigue, the "4-Steps to control your fatigue" (4-STEPS) program. In this intervention program, the combination of graded exercise and pacing is incorporated [22]. The development and evaluation of brief interventions is important because of the time, money and energy consuming efforts associated with longer interventions.

The main objective of the study is to evaluate the efficacy of the 4-STEPS program in promoting physical activity and in reducing fatigue.

Methods/Design

Design of the study

This is a two-arm multi-centre randomised controlled trial in patients who meet operationalised criteria for either ICF or CFS. It consists of a 3-month intervention and a 12-month follow-up phase (Figure 1). There are 3 measurement points: baseline, post-test (3 months) and follow-up at 12 months.

Approval for the trial was obtained from the Ethics Committee of the North Regional Health Administration (Ref: 27.09), from the

directors of each participating health care institution and from the Portuguese Fibromyalgia and Chronic Fatigue Syndrome Patient Association.

Setting
The trial, including measurements and intervention sessions is conducted in five Portuguese primary care centres, in a private practice clinic and at the Portuguese Fibromyalgia and Chronic Fatigue Syndrome Patient Association.

Participants
Patients attending their physician with a main complaint of unexplained fatigue of at least six months duration are recruited for the study. Inclusion criteria are: meeting the operationalised criteria for ICF or CFS (CDC criteria) [6]; aged between 18 and 65; fluent in spoken Portuguese; capacity to provide informed consent. Exclusion criteria are: presence of a concurrent somatic condition which can explain the fatigue symptoms; patients with severe psychiatric disorders.

Power calculation
The sample size was calculated based on the primary outcome (fatigue severity). A power calculation [32], using an independent samples t-test (5% level of significance) indicated that a sample size of 34 will have 80% power to detect a mean difference of 7 points [33, 34] between the intervention and the control group, on the subjective experience of fatigue subscale of the Checklist of Individual Strength (CIS-R) [35].
Anticipating a drop-out rate of 20% [33], we aim at recruiting 41 subjects per group at baseline.

Randomization method
Participants are recruited from consecutive referrals and allocated to one of the two trial arms by the research team leader. Randomisation sequence is stratified by centre with a 1:1 allocation to the two treatment arms. Standard care is given to all participants and the intervention group additionally receives the 4-STEPS program.

Enrolment procedure
Different procedures are followed for recruiting patients from the primary health care institutions on the one hand and from the patient association on the other.

Health care institutions
First, patients that meet the inclusion/exclusion criteria are approached for participation by their primary care physician. Secondly, the physician provides a brief explanation of the study to the patient and asks for the patient's authorization to be contacted by a member of the research team. Third, patients receive information from the principal investigator about the trial and what their participation involves. Finally, patients are assigned to either the intervention or the control condition by randomized sampling. All patients willing to participate sign a written informed consent before being enrolled in the study.

National Fibromyalgia and Chronic Fatigue Patient Association
Initially, a letter containing information about the trial, what participation involves and the written informed consent form is sent to all members of the association from the Lisbon and Porto region that meet the inclusion/exclusion criteria and have previously indicated they were available for participation in research studies. Patients who wish to participate in the study return the written informed consent and are subsequently randomly assigned to either the intervention or the control group.

Interventions

Control Group
In addition to standard medical care, patients that are assigned to this group receive a flyer with information about the general health benefits of physical activity and the current physical activity guidelines for adults [13].

Intervention Group
In addition to standard care, patients in the intervention group receive the 4-STEPS program that consists of:

• Two face-to-face individual motivational interviewing (MI) sessions aimed at exploring important health and life goals, increasing participants' motivation and confidence to be physically active and setting a specific personal physical activity goal. The first MI session takes place 1 week after the baseline assessment and the second MI session takes place 2 weeks after the first. The MI session is delivered by a psychologist with MI training (member of the research team). The duration of the sessions is approximately 1 hour. Details on the topics addressed in the MI sessions are presented in Table 1.
• Two brief telephone counseling sessions: These sessions take about 20 minutes and are provided 2 weeks and 6 weeks after the last MI session. Details on the topics addressed during the telephone sessions are presented in Table 1.
• Self-regulation (SR) booklets: There are two booklets that are designed to help patients change their level of physical activity (Informational booklet and Workbook). The Informational booklet is provided at the end of the baseline assessment, the "Step 1" part of the Workbook is provided at the first MI session and the parts "Step 2", "Step 3" and "Step 4" are given during the second MI session. Details on the topics that are addressed in the SR booklets are presented in Table 2.
• A pedometer to register physical activity on a daily basis (steps taken) during the 3 month intervention period. Instructions on how to use the pedometer are given in the baseline assessment session (Table 2).
• Daily activities record (Table 2): Patients receive several daily activity records (physical activities, mental activities and rest). The first daily activity record is given to the patient at the end of the first MI session; patients are asked to fill out the activity record in the time period between the first and second MI session. This homework assignment aims at evaluating the patients' daily activities management and possibly recognizing an erratic pattern of rest and activity (boom and bust cycle). At the end of the second MI session, patients receive daily activities records that can be used to monitor changes in daily activity patterns during the subsequent nine weeks.
• Leaflet for family (Table 2): At the end of the first MI session

patients receive a leaflet for their partner or significant other in order to increase social support.

Assessments

Measures will be collected at baseline, 3 months later and 12 months after baseline. All measures are self-report. Data will be collected in both the health care institutions and the patient association, at all times (Table 3). Primary and secondary outcomes, predictors and process evaluation measures are described below. A description of measures and time points can be found in Table 3.

Primary Outcome

The primary outcome is the reduction of perceived fatigue severity, which is assessed by means of the Checklist of Individual Strength (CIS-20R) [35]. A difference of 7 points between the intervention and the control group on the main dimension (= the subjective feeling of fatigue subscale) of the CIS-20 R is considered to be a clinically significant difference [33, 34].

Secondary Outcomes

- Fatigue severity, assessed by means of the CIR-20R [35].
- ICF and CFS diagnosis will be assessed by means of the CDC criteria and using the CDC-CFS Symptom Inventory [36].
- Presence of Fibromyalgia symptoms.
- Fatigue impact is assessed by means of a modified version of the pain interference subscale of the Brief Pain Inventory (BPI) [37].
- Work or daily activities related fatigue is assessed by means of the Need for Recovery Scale (NFR) [38].
- Use of health care resources is measured on the basis of two questions: (1) number of visits to the primary care physician and medical specialists, (3) use of medication.
- Work related information: currently (not) working, if currently working, number of hours working, working part-time due to fatigue, dropped out of work due to fatigue, number of days absent from work.
- The All-or-nothing and Limiting behaviour scales from The Behaviour Responses to Illness Questionnaire (BRIQ) [39] are used to assed behavioural symptom management.

•Anxiety and depression are measured with the Brief Symptom Inventory (BSI) [40, 41].
•Quality of sleep is assessed with five questions based on the DSM-IV criteria for sleep disorders [42] and six questions from the Pittsburgh Sleep Quality Index (PSQI) [43].
•Number and severity of physical symptoms is measured by means of the Patient Health Questionnaire-15 (PHQ-15) [44].
•Physical and emotional functioning is measured with the Short Form Health Survey-12 (SF-12V.2) [45].
•Physical activity: two different measures are used to assess physical activity level. The first is the pedometer (YAMAX SW-200), a portable device that counts the number of steps taken, by detecting hip motions. Participants are asked to use the pedometer on a daily basis for seven consecutive days and register their daily number of steps on a form that is provided to the patient. The second measure is the Sports subscale of the SQUASH [46]; in this subscale participants indicate the type of physical activity they do (e.g. swimming) including the frequency per week (e.g. 3 days per week) and duration per day (e.g. 50 minutes) for each of these activities. The intensity of each of these activities is calculated based on the Ainsworth's Compendium of Physical activities [47].

Predictors

•Demographic information (age, gender and education).
•Presence of a severe infection prior to the onset of fatigue.
•Duration of fatigue at baseline.
•Occurrence and current impact (by means of a Visual Analogue Scale from 0cm- no impact at all to 10cm-exterme impact) of a serious life event experienced prior to the onset of fatigue.
•Patients' illness beliefs are assessed by the Brief Illness Perception Questionnaire (Brief IPQ-R) [48].
•Three subscales of the Cognitive Emotion Regulation Questionnaire - Short Version (CERQ-short) [49] were used to assess adaptive cognitive coping strategies, and a version of the Pain Catastrophizing Scale (PCS) adapted for fatigue [50] was used to measure catastrophic cognitions related to CF symptoms.
•Level and range of social support are assessed.
•Goal progress and self-regulation skills to achieve a personal goal are measured with the Self-regulation Skills Battery (SRSB) [51].

•Self-efficacy to overcome obstacles to physical activity is assessed with the Barriers Efficacy Scale [52].
•Autonomous and Coerced motivation to be physically active is assessed using the respective scale from the Treatment Self-regulation Questionnaire (TSRQ) [53].
•Physical activity intention, action planning and coping planning are assessed using the measures from Sniehotta and colleagues [54].

Process evaluation
Participant satisfaction with the self-regulation based 4-steps program will be assessed.

Analysis plan
We will use the SPSS and AMOS software packages for data analysis. Descriptive analysis will be performed for demographics, clinical information and process evaluation, stratified by treatment condition. Differences between the control and intervention group for the primary and secondary outcome measures will be assessed using MAN(C)OVA and AN(C)OVA. We also intend to use regression analysis and structural equation modelling to analyse longitudinal relationships between predictors, possible mediators and outcomes (path analysis).

Discussion

Physical activity seems to be very important for patients suffering from unexplained chronic fatigue, while SR interventions seem to be effective in promoting long-term health behaviour change. The 4-STEPS program will be the first brief SR based physical activity intervention for ICF/CFS patients. We are not aware of any RCT to promote physical activity in these patients conducted in Portugal. This RCT will provide information on the efficacy of the intervention as well as on the predictors of physical activity, fatigue and other somatic symptoms. The fact that it is a brief intervention, that requires minimal personal contact with the health care

professional and that patients receive self-help materials to support them can also be seen as an advantage from a cost-effectiveness point of view if the trial has a significant effect. If proven effective, this program can be considered as an adjunctive treatment for ICF/CFS.

Status of the trial

The 4-STEPS recruitment started in January 2011 and it is ongoing.

List of abbreviations

CFS Chronic Fatigue Syndrome
CBT Cognitive Behavioural Therapy
GET Graded Exercise Therapy
ICF Idiopathic Chronic Fatigue
ISRCTN International Standard Randomised Controlled Trial
MUPS (Medically Unexplained Physical Symptoms)
RCT Randomised Controlled Trial
SR Self-regulation
4-STEPS: "4 Steps to control your fatigue" program

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MM, VDG and SM contributed to the design of the study and the creation of the Support materials. VDG, SM and IL participate in the study coordination. MM wrote the draft version of the manuscript. All authors reviewed and approved the final manuscript.

Acknowledgements

This study was carried out as part of a grant from the Portuguese Foundation for Science and Technology to the first author (SFRH/BD/47579/2008).

The authors would like to thank Maria João Gouveia for her contribution to the support materials.

References

1. Puetz TW: Physical activity and feelings of energy and fatigue: epidemiological evidence. *Sports Medicine* 2006, 36(9):767-780.
2. Torres-Harding S, Jason LA: What is fatigue? History and epidemiology. In *Fatigue as a window to the brain*. Edited by DeLuca J. Cambridge: MIT Press; 2005:3-17.
3. Wessely S: Foreword. In *Fatigue as a window to the brain*. Edited by DeLuca J. Cambridge: MIT Press; 2005: x-xvii.
4. Afari N, Buchwald D: Chronic Fatigue Syndrome: A review. *American Journal of Psychiatry* 2003, 160:221-236.
5. Huibers MJH, Berskans AJHM, Van Schayck CP, Bazelmans JFM, Knothneurs JA, Bleijenberg G: Efficacy of cognitive behavioral therapy by general practitioners for unexplained fatigue among employees: randomized controlled trial. *British Journal of Psychiatry* 2004, 184:240-246.
6. Fukuda K, Strauss SE, Hickie I, Sharpe MC, Dobbins, JG, Komaroff A: The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of Internal Medicine* 1994, 121:953-959.
7. Campling F, Sharpe M: *Chronic Fatigue Syndrome (CFS/ME).* 2nd edition. Oxford: Oxford University Press; 2008.
8. Cairns R, Hotpof M: Prognosis of chronic fatigue syndrome: a systematic review. *Occupational Medicin*e 2005, 55:20-31.
9. Prins JB, Vand der Meer JWM, Bleijenberg G: Chronic fatigue syndrome. *The Lancet* 2006, 367:346-355.
10. Fulcher KY, White PD: Strength and physiological response to exercise in patients with chronic fatigue syndrome. *Journal of Neurology and Neurosurgery Psychiatry* 2000, 69:302-307.
11. Berne K: *Chronic Fatigue Syndrome, Fibromyalgia and Other Invisible Illnesses: The Comprehensive Guide*. Alameda, CA: Hunter House Publishers; 2002.
12. National Institute for Health and Clinical Excellence: *Guideline 53: chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy)*. London, 2007.
13. American College of Sports Medicine: *ACSM's guidelines for exercise testing and prescription.* 8th revised edition. Baltimore; 2019.
14. Fulcher KY, White PD: Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ* 1997,

314(7095):1647-52.
15. Wallman KE, Morton AR, Goodman C, Grove R, Guilfoyle AM: Randomised controlled trial of graded exercise in chronic fatigue syndrome. *Medical Journal of Australia* 2004, 180(9):444-448.
16. McGuire L, Edmonds L, Price JR: Exercise Therapy for Chronic Fatigue Syndrome. *Cochrane Database Syst Rev* 2004, 3:CD003200.
17. Moss-Morris R, Sharon C, Tobin R, Baldi JC: A randomized controlled graded exercise trail for chronic fatigue syndrome: outcomes and mechanisms of change. *Journal of Health Psychology* 2005, 10(2):245-259.
18. Ridsdale L, Darbshire L, Seed PT: Is graded exercise better than cognitive behavior therapy for fatigue? A UK randomized trial in primary care. *Psychological Medicine* 2004, 34:37-49.
19. Price JR, Mitchell E, Tidy E, Hunot V: Cognitive behaviour therapy for chronic fatigue syndrome in adults. *Cochrane Database Syst Rev* 2008, 3:CD001027.
20. Burgess M, Chalder T: *Overcoming Chronic Fatigue*. London: Constable & Robinson; 2005.
21. NHS Foundation Trust and St. Bartholomew's Hospital*: Graded Exercise Therapy: A self-help guide for those with chronic fatigue syndrome/myalgic encephalomyelitis*. London; 2009.
22. Nijs J, Paul L, Wallman K: Chronic fatigue syndrome: an approach combining self-management with graded exercise to avoid exacerbations. *Journal of Rehabilitation Medicine* 2008, 40:241-247.
23. White PD, Sharpe MC, Chalder T, DeCesare JC, Walyin R: Protocol for the PACE trial: a randomised controlled trial of adaptative pacing, cognitive behaviour therapy and graded exercise as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy. *BMC Neurology* 2007, 7:6.
24. De Gucht V, Maes S: Explaining medically unexplained symptoms: toward a multidimensional theory-based approach to somatisation. *Journal of Psychosomatic Research* 2006, 60:349-35.
25. Deary V: A precarious balance: using a self-regulation model to conceptualize and treat chronic fatigue syndrome. *British Journal of Health Psychology* 2008, 13: 231-236.
26. Maes S, Gebhardt W: The health behavior goal model. In *Handbook*

of Self-regulation. Edited by Boekaerts M, Pintrich PR, Zeidner M. San Diego, CA: Academic Press; 2000:343-368.
27. Maes S, Karoly P: Self-regulation assessment and intervention in physical health and illness: a Review. *Applied Psychology: An International Review* 2005, 54(29):267-299.
28. Miller WR, Rollnick S: *Motivational Interviewing: Preparing People for Change*. New York: Guilford Press; 2000.
29. Resnicow K, DiIorio C, Soet JE, Borrelli B, Hecht J: Motivational interviewing in health promotion: it sounds like something is changing. *Health Psychology* 2002, 21(5):444-451.
30. Powell P, Bentall RP, Nye FJ, Edwards RHT: Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. *BMJ* 2001, 322:387.
31. Ang D. Kesavalu R, Lydon JR, Lane KA, Bigatti S: Exercise-based motivational interviewing for female patients with fibromyalgia: a case series. *Clinical Rheumatology* 2007, 26(11):1843-9.
32. Faul F, Erdfelder E, Lang AG, Buchner A: G*Power 3: a flexible statistical power analysis program for the social, behavioural and biomedical sciences. Behavior Research Methods 2007, 39:175-191.
33. Knoop H, Van der Meer JW, Bleijenberg G: Guided self-instructions for people with chronic fatigue syndrome: a randomised controlled trial. *British journal of Psychiatry* 2008, 190:340-341.
34. Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G: Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. *BMJ* 2005, 330(7495):820.
35. Vercoulen JHMM, Alberets M, Bleijenberg G: De Checklist Individual Strenght (CIS). *Gedragstherapie* 1999, 32:31-36.
36. Wagner D, Nisenbaum R, Heim C, Jones JF, Unger ER, Reeves WC: Psychometric properties of the CDC symptom inventory for assessment of chronic fatigue syndrome. *Population Health Metrics* 2005, 3:8.
37. Cleeland CS, Ryan KM: Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singapore* 1994, 23:129-138.
38. Van Veldhoven M, Broersen S: Measurement quality and validity of the "need for recovery scale". *Occupational Environmental Medicine* 2003, 60(Suppl 1):3-9.
39. Spence M, Moss-Morris R, Chalder T: The behaviour responses to illness questionnaire (BRIQ): a new predictive measure of medically unexplained symptoms following acute infection. *Psychological*

Medicine 2005, 35:583-593.
40. Degoratis, L.(1993). *Brief Symptom Inventory: Administration, Scoring and Procedures Manual*. 4th edition. Minneapolis: National Computer System.
41. Canavarro MC: Inventário de sintomas psicopatológicos – BSI. In *Testes e provas psicológicas em Portugal. Volume 2*. Edited by Simões M, Gonçalves M, Almeida L. Braga: SHO/APPORT; 1999:87-109.
42. American Psychological Association: *Diagnostic and statistical manual of mental disorders (DSMIV-TR)*. 4th edition. Washington DC; 2000.
43. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: The pittsburgh sleep quality index (PSQI): a new instrument for psychiatric research and practice. *Psychiatry Research* 1989, 28(2):193-213.
44. Kroenke K, Spitzer R, Williamsm JBW: The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. *Psychosomatic Medicine* 2002, 64:258-266.
45. Ware JE, Kosinski M, Turner-Bowker DM, Gandek B: *How to score version 2 of the SF-12® Health Survey*. Lincoln, RI: Quality Metric Incorporated; 2002.
46. Wendel-Vos GCW, Schuit AJ, Saris WHM, Kromhout D: Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. Journal of Clinical Epidemiology 2003, 56, *1163 – 1169*.
47. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR, Schmitz KH, Emplaincourt PO, Jacobs DR, Leon AS: Compendium of physical activities: an update of activity codes and MET intensities. *Medicine and Science of Sports & Exercise* 2000, 32(Suppl 9):498-504.
48. Broadbent E, Petrie KJ, Main J, Weinman J: The brief illness perception questionnaire. *Journal of Psychosomatic Research* 2006, 60:631-637.
49. Garnefski N, Kraaij V: Cognitive emotion regulation questionnaire: development of a short 18-item version (CERQ-short). *Personality and Individual Differences* 2006, 41:1045-1053.
50. Sullivan MJL, Bishop SR, Pivik J: The pain catastrophizing scale: development and validation. *Psychological Assessment* 1995, 7:524-532.
51. Maes S, Karoly P, De Gucht V, Ruehlman LS, Heiser W: *The self-regulation skills battery (SRSB)*. Leiden(NL)/Phoenix (AZ): Leiden

University & Arizona State University; 2006.
52. Marques M, Gouveia MJ: Portuguese version of the physical activity barriers efficacy questionnaire. In *Proceedings of the Sixth National Conference on Health Psychology*: 2 - 4 February 2006; Faro. Edited by Leal I. Ribeiro JPL, Jesus SN. Edições ISPA; 1996: 497-501.
53. Williams GC, Freedman ZR & Deci EL: Supporting autonomy to motivate glucose control in patients with diabetes. *Diabetes Care* 1998, 21:1644-165.
54. Sniehotta FF, Scholz U, Lippke S, Ziegelmann J: *Scale for assessment of implementation planning and coping planning.* 2002. [http://userpage.fuberlin.de/~falko/scales/heartdocu.html]

Figure 1 Recruitment and Design Flow Diagram

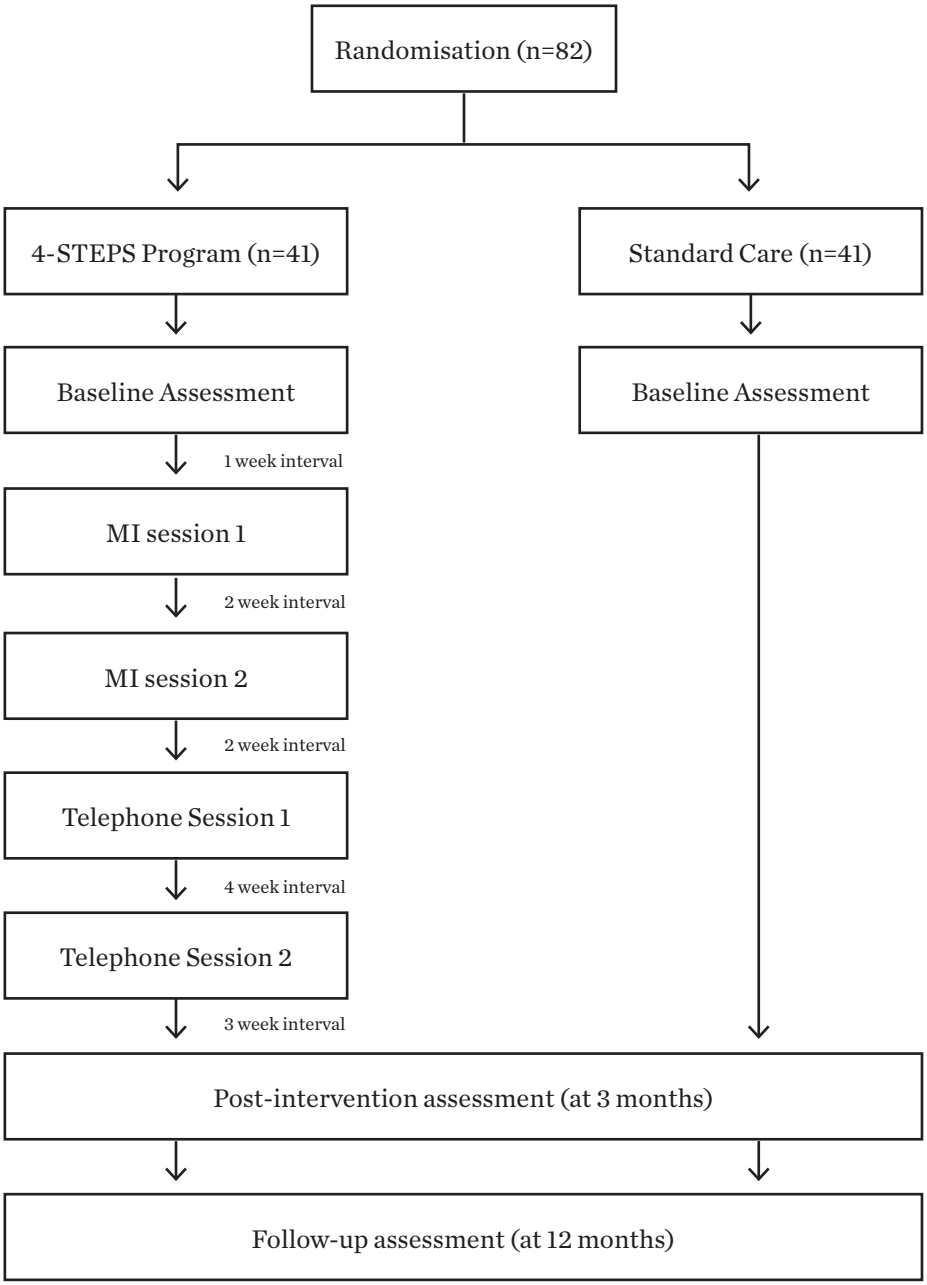


Table 1 4-STEPS Sessions content

4-STEPS sessions	Topics
Motivational Interviewing Session 1	✓ Listen to patient complaints, with emphasis on fatigue. ✓ Illness perceptions. ✓ Exploration of patients' present physical activity behavior. ✓ Current health behaviors and other activities are explored (physical activity, sleep, pain, etc.). ✓ Discussion of the information on the booklet given previously (specially the relation between CF major symptoms and physical activity behavior and boom-bust pattern). ✓ Motivation and Confidence Scales: Exploration of the willingness to engage in physical activity (or adjust current physical activity behavior) and the confidence in one's own capability to achieve this behavior with success. ✓ Discussion of the pros and cons (not-) to change physical activity behavior (Decisional Balance). ✓ Social support network is addressed.
Motivational Interviewing Session 2	✓ Discussion of possible competing goals with physical activity (e.g. housework chores). ✓ Strategies to overcome obstacles to physical activity and competing goals are addressed. ✓ Based on the register of daily activities and steps taken (pedometer register) and GET scheme for physical activity, the patient establishes a personal physical activity goal for the following two months. ✓ Discuss the possible reasons for perpetuation of symptoms and difficulty to change health behaviors in CF patients, namely perfectionism, fear of movement, presence of stressful situations and boom-bust pattern. (some are already mentioned at the first motivational interview and are now emphasized). ✓ Exploration of emotion control importance and techniques (e.g. relaxation techniques).
Telephone sessions:	✓ Revision of the physical activity goal planning (adequacy to the patients' present situation). ✓ Relapse prevention (strategies to overcome new or persisting difficulties to physical activity and emotion control strategies).

Table 2 4-STEPS Materials content

4-STEPS materials	Topics
Self-regulation Informational booklet	✓ Overview of Chronic Fatigue: CDC diagnosis criteria, epidemiology information, etiology, possible factors that contribute to a better or words prognosis (e.g. physical inactivity/activity). ✓ Physical activity: current physical activity guidelines for adults in general population, physical and psychological benefits of physical activity, benefits of physical activity for CF. Information about different types of physical activities (that are appropriated for CF) such as walking as well the importance and illustration of relaxation training. ✓ Link between CF symptoms and physical (in-) activity (deconditioning cycle) and boom-bust pattern (erratic pattern of rest and activity).
Self-regulation Workbook	*STEP 1 – "Am I ready to start?"* ✓ Motivation and Confidence Scales: Patients' willingness and confidence to do adjusted levels of physical activity is assessed on a scale for ranging from 0% (not at all) to 100% (very much). ✓ Decisional Balance: list of the pros and cons (not-) to change in relation to physical activity. ✓ Competing goals with exercise: information on the importance o analyzing possible competing goals (or conflicting activities) with exercise that may be refraining patients from physical activity. List of two main activities (e.g. other leisure activities). ✓ Activity/Rest Diary and Pedometer log – instructions to use for two weeks (interval between MI sessions) and the importance of the pedometer as a motivational strategy. *STEP 2 – "My physical activity goal":* ✓ GET Scheme and daily activity management: information on the importance of increase physical activity level gradually, consider the way patients feel in different days (different levels if patients is feeling good or bad), importance of rest during physical activity, importance of adjusting physical activity levels to the amount of effort spent in that day (balance between activities and rest). ✓ Goal setting activity: explanation of how to set a goal (SMART – specific, measurable, achievable, realistic and timely), formulation of a personal physical activity goal to achieve in 2 months time (e.g. to do brisk walking four days per week for 30 minutes (plus 10 minutes break), implementation intentions (type of activity, frequency and intensity, period of the day, with whom, where) and a goal ladder (patients formulate goals for every 2 weeks until reaching the two months time and main goal. ✓ Information on self-rewarding for each step goal achieved. ✓ Tips for managing daily activities and incorporate physical activity on the daily routine *STEP3 – "Overcoming obstacles":* Problem solving activity: List two main physical activity barriers and a strategy to overcome it. *STEP 4 – "I am physically active...and I want to keep that way":* ✓ Relapse prevention information and strategies. ✓ *Resources and support for CF and physical activity.*
Pedometer Record	✓ Similar to the record used for the assessment (day of the week and number of steps for each day).
Daily activities record	✓ Record containing the days of the week and hours each day. Patients fill the activities they do in each hour of day. The options are: physical activities, other activities (activities requiring mental effort) and rest. Each option is explained in detail.
Leaflet for family	✓ Facts about CF. ✓ Brief information on the relation between physical activity and CF. ✓ Tips for partners or other relatives to support patients with CF.

Table 3 Measures to be administered at each time point

	Baseline	Post-test	12-months
Demographics	X		
Severe infection	X		
Life event	X		
Medical advice	X		
Duration Symptoms and diagnosis	X		
CFS symptom checklist	X	X	X
Presence of FM symptoms	X	X	X
CIS-20R	X	X	X
Impact of fatigue	X	X	X
NFR	X	X	X
Work related questions	X	X	X
Brief IPQ-R	X	X	X
Brief IPQ-R causes subscale	X		
CERQ positive subscales	X	X	X
PCS	X	X	X
BRIQ	X	X	X
Social support	X	X	X
BSI	X	X	X
Sleep	X	X	X
PHQ-15	X	X	X
SF-12	X	X	X
Physical Activity history	X	X	X
Steps taken (pedometer)	X	X	X
Physical activity intention	X		
Action planning	X		
Coping planning	X		
SRSB Physical activity goal elicitation	X		
SRSB Physical activity goal progress	X	X	X
SRSB goal efficacy scale	X		
SRSB all scales		X	X
Barriers Efficacy	X	X	X
TSRQ	X	X	X
Intervention evaluation (intervention condition)		X	

06

Effects of a self-regulation based physical activity program (the "4-STEPS") for unexplained chronic fatigue: a randomized controlled trial.

Manuscript published
M. Marques, V. De Gucht, I. Leal & S. Maes (2014) Effects of a self-regulation based physical activity program (the "4 -STEPS") for unexplained chronic fatigue: A randomized controlled trial. *International Journal of Behavioral Medicine*. doi: 10.1007/s12529-014-9432-4

Abstract

Purpose: This study aimed at assessing the effects of a self-regulation based brief physical activity program for patients suffering from unexplained chronic fatigue, the "4-STEPS to control your fatigue program".
Methods: A 12-week randomized controlled trial was conducted. Adult patients meeting the CDC criteria for idiopathic chronic fatigue were randomized to either the control condition (standard care) or the intervention condition (4-STEPS). The 4-STEPS was based on self-regulation principles and consisted of motivational interviewing and self-regulation skills training. All patients were assessed at baseline and post-treatment (12 weeks) for fatigue severity (primary outcome) and impact, physical activity (leisure-time physical activity, number of daily steps, and personal activity goal progress), health-related quality of life, somatic distress and psychological distress (depression and anxiety).
Results: Ninety-one patients (45 intervention and control patients) received the allocated intervention. At post-treatment, statistical analysis revealed a significant difference for subjective experience of fatigue (4.73 points; g=0.51) in favor of the intervention group. Mixed design ANCOVAs showed a significant effect of the 4-STEPS on fatigue severity, leisure-time physical activity, personal activity goal progress and health-related quality of life. No significant effects were found for number of daily steps and somatic and psychological distress.
Conclusions: The 4-STEPS program has significant beneficial effects at post-treatment. This brief self-regulation based intervention looks promising for the management of unexplained chronic fatigue.

Trial Registration: ISRCTN70763996

Keywords: chronic fatigue, randomized controlled trial, physical activity, self-regulation.

Introduction

Unexplained or Idiopathic Chronic fatigue (ICF) is a condition characterized by the presence of severe and persistent fatigue (lasting for at least 6 months) that cannot be explained by an organic disease. According to the Centres for Disease Control and Prevention (CDC), persistent fatigue is diagnosed as Chronic Fatigue Syndrome (CFS) on condition that a minimum number of additional somatic symptoms are present [1]. CFS is a serious medical condition in which the patient's functioning is significantly impaired leading to disability and lower health-related quality of life (HRQoL) [2]. One of the major symptoms is the presence of post-exertional malaise, which is characterized by severe exhaustion following physical activity. Patients' perceptions and expectations related to symptom exacerbation as a consequence of exercise can lead to fear of physical exercise and can, therefore, explain the reduced levels of physical activity found in these patients [3, 4]. In addition, several studies emphasize the fact that the lack of physical activity and excessive resting found in these patients can result in physical deconditioning and, as a consequence, perpetuate fatigue severity and physical disability [4-6]. Therefore, (balanced) physical activity has been considered to be an important behaviour in managing chronic fatigue [7].

Graded Exercise Therapy (GET), a behavioural intervention targeting a gradual increase in aerobic exercise (in order to avoid overexertion), has been shown to have beneficial effects on fatigue severity in CFS patients [8]. Cognitive behavioural therapy (CBT), which usually incorporates changes in physical activity (and rest) behaviour, has also demonstrated to be effective in reducing fatigue symptoms in CFS patients [9]. A recent meta-analysis compared the effectiveness of GET and CBT [10]. Both were moderately effective in reducing fatigue and functional impairment. Still, results were heterogeneous.

Both CBT and GET interventions are usually resource-intensive requiring a considerable number of contact hours and sessions (in general between 8 and 16 sessions) with patients [10, 11]. Recently, two randomised controlled trials that tried

to overcome this limitation by conducting minimal contact CBT interventions based on self-guided instruction manuals and regular email contacts, showed promising results [12, 13]. Another intervention study (pragmatic rehabilitation) targeting physical activity for chronic fatigue patients, comparing treatment conditions that differ in intensity, found that the minimum intervention conditions (2 face-to-face sessions with or without 7 brief telephone contacts) were as successful as a more extensive version of the program (9 face-to-face sessions) [14].

Adopting a health behaviour change framework, such as Self-regulation (SR) theory [e.g. 15] can be useful for promoting physical activity in chronic fatigue patients [16, 17]. SR based interventions have demonstrated to be effective in promoting health behaviour change in chronic disease populations [17-20]. According to SR theory behavior is a goal guidance process [16]. This process consists of a goal selection/ goal setting or motivational phase, an active goal pursuit or action phase and a goal attainment or maintenance phase. Several SR cognitions and skills are guiding this process, such as autonomous regulation of behavior (and goal ownership), self-efficacy, goal-setting, planning, self-monitoring, feedback, emotional and attention regulation and relapse prevention strategies [16].

An important form of intervention that incorporates SR principles is Motivational interviewing (MI), which is a "collaborative conversation style for strengthening a person's own motivation and commitment to change" ([21] p. 12). In MI, the patient's own motivation for change is evoked and self-efficacy is strengthened. MI was found to be effective in promoting health behavior change, especially in helping patients move from ambivalence towards behavior change during a motivational phase [21, 22]. While MI mainly focuses on SR cognitions, SR skills are equally important, especially during the active goal pursuit and maintenance phase [16].

From this perspective, we developed a brief SR based intervention, combining MI and SR- skills training, to target physical activity among patients with unexplained chronic fatigue (the "4-STEPS to control your fatigue" program). This study aimed at evaluating the effects of the 4-STEPS program

upon fatigue severity and impact, physical activity, health-related quality of life, somatic distress and psychological distress.

Method

The rationale and details of the trial design were given in detail elsewhere [23] and will thus only be briefly summarized here.

Trial design

This was a 12-week parallel-group, multicentre randomized controlled trial, with equal randomisation (1:1) to either the intervention condition (4-STEPS program) or the control condition. Randomisation sequence was stratified by sample (Health Care centres and Patient Association), and within the first sample also by centre. Randomisation was conducted using computer-generated allocation numbers, under the supervision of a member of the research team, who did not take part in the subsequent phases of the trial. Group allocation was known to subjects, therapist and assessors. Patients were recruited from consecutive referrals. Patients were assessed at baseline (T1) and 12-weeks later (post-treatment – T2). The primary outcome was subjective experience of fatigue and secondary outcomes were fatigue severity, fatigue impact, physical activity, health-related quality of life (HRQoL- physical and psychological functioning), somatic distress and psychological distress (depression and anxiety). Approval was obtained from the Portuguese Medical-Ethics Committee of the North Regional Health Administration and from the medical board of each participating health care centre. The trial was conducted between January 2011 and December 2012.

Participants and procedure

Adult patients meeting the CDC criteria for idiopathic chronic fatigue (i.e. presenting a main complaint of unexplained fatigue of at least six months duration) were eligible to participate in the study [1]. Additional inclusion criteria were to fully understand and speak Portuguese and to have the capacity to provide an informed

consent. Patients presenting a concurrent somatic condition and/or a severe psychiatric disorder that could explain fatigue symptoms (according to the CDC criteria for exclusionary medical and psychiatric conditions [1]) were excluded.

The study was conducted in several Portuguese health care institutions (four public primary care centres and one private practice) and in the Portuguese Fibromyalgia and Chronic Fatigue Syndrome Patient Association. Based on the inclusion and exclusion criteria, patients from the health care centres were referred by their medical doctor. All patients were informed of the trial content and invited for an individual interview in the health care centre (baseline assessment). Patients from the patient association who met the criteria (i.e. clinical diagnosis of unexplained chronic fatigue) and previously indicated their willingness to participate in research received an institutional letter containing the details of the trial. Patients who wished to participate returned the written informed consent form and were invited for the baseline assessment. For both samples, the inclusion and exclusion criteria were checked by the research team, using self-report measures based on the CDC criteria. In addition to standard medical care, patients assigned to the control condition received a flyer with information about the general health benefits of physical activity and current physical activity guidelines for adults [24], and set a personal physical activity goal for the upcoming months. Participants assigned to the intervention condition additionally received the 4-STEPS program.

4-STEPS to control your fatigue

The 4-STEPS program consisted of a brief SR based intervention to promote physical activity in chronic fatigue patients. The intervention was delivered by one trained health psychologist (with motivational interviewing training) to individual patients. The intervention was structured around the SR phases of goal pursuit (goal selection and setting, active goal pursuit and goal attainment, maintenance and disengagement) [17].

Firstly, participants received two 1-hour face-to-face individual motivational interviewing sessions (weeks 1 and 3) aimed at: (a) exploring important health and life goals, to which a physical

activity goal could be related, (b) increasing participants' motivation and confidence to be physically active and (c) setting a specific personal physical activity goal. This personal and flexible physical activity goal, which took into consideration the need to avoid overexertion, was set by each patient during the second MI session. Patients also formed action plans regarding their goal (i.e. which physical activities would be done, and when, where, for how long and with whom each would take place).

Secondly, participants received an informational booklet (available from the first author) containing information regarding: (a) the diagnosis of CF(S), (b) factors contributing to a better or worse prognosis, and (c) the link between CF(S) symptoms and physical (in-)activity and the boom-bust pattern (i.e. erratic pattern of rest and activity) commonly found in these patients.

Thirdly, a SR based workbook (available from the first author) was given to patients. The SR workbook was divided in four steps, each one focusing on specific SR cognitions and skills: Step 1-"Am I ready to start?" (focusing on self-efficacy, motivation, and control over competing goals), Step 2- "My physical activity goal" (focusing on goal-setting, action planning and self-monitoring), Step 3 "Overcoming obstacles" (focusing on coping efficacy and planning, feedback, and attention and emotion regulation i.e. control of distracting stimuli and negative emotions to maintain a focus on goal pursuit), and Step 4 "I am physically active...and I want to keep it this way" (focusing on relapse prevention, including coping efficacy and planning and goal reformulation).

Fourthly, patients received two brief SR-based telephone-counselling sessions (weeks 5 and 9). This telephone support aimed at reviewing the participants' physical activity goal and providing relapse prevention strategies.

Fifthly, patients received a pedometer to register steps taken on a daily basis during the 12-week intervention period. Finally, patients received a leaflet for their partner or significant other with relevant information on chronic fatigue, the objective of which was to increase social support.

Outcomes

Patient characteristics Socio-demographic characteristics included age, gender, education and employment status. Clinical information was gathered using the following indicators: (1) presence of persistent fatigue, (2) duration of fatigue symptoms, (3) impact of fatigue on daily activities (4) whether fatigue was alleviated by rest, (5) number of medical consultations, and (6) a CDC based symptom checklist for CFS [25]. The checklist presents 19 major and minor symptoms of CFS as defined by the CDC criteria [1]. Respondents are asked to rate if they experienced each of the symptoms for the last 6 months. For the purpose of this study a dichotomous scale (Yes/No) was used. A major symptom score is calculated by adding up the number of major symptoms presented (ranging from 1 to 8). To be diagnosed with CFS patients need to have a complaint of persistent unexplained fatigue (at least 6 months) that leads to a significant disability and to have at least 4 of the major CFS symptoms listed by the CDC. Patients not fulfilling the full criteria were classified as ICF patients. The self-reported measures also included a question regarding the presence of chronic disease and/or psychiatric disease, as well as name and duration, if any.

Fatigue Severity was assessed at T1 and T2 by means of the Portuguese adaptation of the Checklist of Individual Strength (CIS20-P) [26], which is a well-validated and reliable measure for assessing fatigue severity in chronic fatigue patients [27] {Vercoulen, 1999, De Checklist Individual Strenght (CIS);Marques M, , Psychometric properties of the Portuguese version of the Checklist of Individual Strength (CIS20-P)}. The CIS20 is a 20 item self-report measure that assesses four dimensions of fatigue: *subjective experience of fatigue, concentration, motivation* and *activities*. Items are rated on a 7-point scale. A total score (total fatigue severity) can be calculated by adding up the scores for each dimension. For the purpose of this study only the subjective experience of fatigue dimension (primary outcome; range 8-56) and the total fatigue severity score (range 20-140) were used. Higher scores indicate more fatigue. A cut-off point of 35 on the subjective experience of fatigue dimension of the CIS20 is usually used to define a clinical level of fatigue [28].

Fatigue impact (T1 and T2) was measured by means of a modified version of the pain interference dimension of the well validated Brief Pain Inventory (BPI) consisting of 7 items [29]. Participants were asked to rate on a 10-point scale how their fatigue interfered with several aspects of their life. The total score was used as an outcome. Higher scores indicate a higher fatigue impact (ranging from 0 to 10).

Physical activity (T1 and T2) was assessed by means of:

a) A self-report measure of *leisure-time physical activity* based on the Short Questionnaire to Assess Health-enhancing Physical Activity (SQUASH) [30]. Participants indicate the number of days per week and minutes per day in which they engage in physical activities (bicycling, walking and other activities such as swimming). For each activity of at least moderate intensity (≥3 METs based on the categories of the Ainsworth's compendium of physical activities [31,32]), total minutes of physical activity per week is calculated by multiplying frequency (days/week) and duration (minutes/day). Total number of minutes of leisure-time physical activity (moderate to vigorous physical activity - MVPA) per week is calculated by taking the sum of each activity score.

b) Physical activity was also measured by means of a *pedometer* (T1 and T2). Daily steps were assessed using Yamax Digiwalker SW-200 pedometers, which have been demonstrated to be accurate and reliable [33, 34]. Participants were asked to wear the pedometer for seven consecutive days and register the daily number of steps at the end of each day. The mean of the daily steps over these seven days was used as an outcome measure.

c) *Personal physical activity goal progress.* Using a standardized goal-elicitation procedure, respondents specify a personal physical activity goal which they wish to pursue over the next months. At post-treatment, respondents were reminded of their personal goal and asked to indicate their progress on a 10 cm visual analogue scale (VAS), ranging from "I haven't started yet" (0) to "I have achieved my goal" (10) [35]. Participants of the control group set a personal physical activity goal during the baseline assessment session and participants of the intervention group set their physical activity goal during the second Motivational Interviewing session.

Health-Related Quality of Life *(HRQoL)* (T1 and T2) was

measured using the Short Form Health Survey-12 (SF-12V.2) [36]. The SF-12v2 is a well validated measure that allows to calculate a physical functioning score (Physical HRQoL) and a psychological functioning score (Psychological HRQoL), ranging from 0 to 100, with lower scores representing worse HRQoL.

Somatic distress (T1 and T2) was measured by means of the Patient Health Questionnaire-15 (PHQ-15). The PHQ-15 assesses the presence and severity of 15 somatic symptoms (e.g. back pain). Patients are asked to indicate to what extent they have been bothered in the past 4 weeks by each symptom, with higher scores indicating higher somatic symptom severity (range 0 - 30) [37].

Psychological distress was assessed at T1 and T2 using the Depression and Anxiety subscales from the well-validated and widely used Brief Symptom Inventory (BSI) [38]. Individuals rank each symptom on a 5-point Likert scale (from "never" to "very frequently") with higher scores representing more psychological distress. Scores were calculated by taking the mean of the items of each subscale (range 0-4).

Sample size

An a priori analysis [39] showed that a sample of 34 participants in each group would be sufficient to detect a mean difference of 7 points [12, 40] between the intervention and the control group, on the subjective experience of fatigue dimension of the CIS20-P, with 80% power at a 5% significance level. Considering a possible drop-out of 20% we aimed at recruiting 41 subjects per group.

Statistical Analyses

Descriptive analyses were performed for gender, age, education, employment, clinical information and use of health care resources. Differences between groups at baseline were analyzed using t-tests (for continuous variables) and univariate chi-square tests (for dichotomous variables). The difference in subjective experience of fatigue (primary outcome) between the intervention and control groups at post-treatment was analyzed with an independent samples t-test.

Effects of the intervention on primary and secondary outcomes were examined using 2 (baseline – T1 vs. post-treatment-T2)

x 2 (intervention vs. control) mixed-model repeated measures analysis of covariance (ANCOVA), controlling for setting (Health care centres vs. Patient association) and disease duration. Effect sizes (ES) were the standardized mean difference [(mean a-mean b/ pooled SD)] with Hedge's *g* correction for small samples [41]. Prior to analysis, data was inspected for normality and homogeneity of variance. Leisure-time physical activity was not normally distributed at both time points, and so it was logarithmic-transformed (Lg + 1) for further analyses. Descriptive statistics for this variable are presented in a non-transformed format. Mixed design ANCOVAs were conducted with intention-to-treat analyses (ITT) using the last-observation-carried-forward method (LOCF), which included all participants for whom complete baseline data was available. We undertook sensitivity analyses to test the robustness of the results of the mixed design ANCOVAs using a) Complete Case analysis and b) Multiple Imputation analysis. Five imputation datasets were generated, based on the results from the complete case dataset, using outcome variables as predictors. Linear regression models were adopted for the Multiple Imputation, with the exception of leisure-time physical activity in which we used a Predictive Mean Matching (PMM) approach due to the non-normal distribution of this variable. Assumption that data was missing at random (MAR) was first verified. Each dataset was analyzed individually using mixed design ANCOVAs. Sensitivity analyses revealed similar results for three approaches, with the exception of Psychological HrQoL Therefore main results report the ITT analyses. Missing values at baseline due to incomplete assessment (number of steps per day and goal progress) were also imputed using Multiple Imputation.

Finally, at T2, additional chi-square analyses were conducted for the complete dataset to compare the proportion of patients in each group a) who did not meet non-clinical levels for fatigue severity (<35) assessed by the subjective experience of fatigue sub-scale of the CIS20-P and b) who were physically active. Effect sizes (ES) were Risk Ratio (RR). We considered p values lower than or equal to 0.05 as significant. Data analyses were conducted using the statistical software SPSS v22.

Results

Participant flow and patient characteristics

Among the 165 individuals who were identified as eligible to participate and who were informed about the study, 99 patients were randomised to either the 4-STEPS program or the control condition, and 91 recruited into the trial with adequate baseline measures completed (intervention condition: n= 45; Control condition: n=46). The flow of patients through the trial and reasons for exclusions and withdrawals are displayed in Figure 1.

Demographics and clinical characteristics are presented in Table 1. No significant differences were found for any of the demographics and clinical variables.

Intervention effects

A significant difference of 4.73 points in the subjective experience of fatigue was found between the intervention and the control group (t= -2.46, p=.016, 95% CI – 8.54 to -0.91, g=0.51). Patients in the intervention group presented with lower levels of fatigue severity than those in the control group. At T2, there was no significant difference in the proportion of patients presenting non-clinical levels of fatigue in the intervention (10/35 - 28.6%) and control groups (5/33 - 15.2%; X^2=1.779, p=0.18; RR=1.89 95% CI 0.72 to 4.94). This corresponds to an increase from baseline in the percentage of patients presenting non-clinical levels of fatigue of 25.7% and 6.1%, respectively.

The results of the mixed design ANCOVAs for the ITT (LOCF) approach are presented in Table 2 (for a comparison of results between the three approaches *see* Table 3). There was a significant effect of the intervention on levels of subjective experience of fatigue and total fatigue severity, after controlling for the effect of the covariates (p=.028 and p=.019; respectively). In the intervention group there was a significant decrease from T1 to T2 in the subjective experience of fatigue (mean change=-3.38, 95% CI -5.81 to -0.94; control group mean change= +0.35, 95% CI -1.89 to 2.58) and total fatigue severity (mean change=-4.67, 95% CI –9.61 to 0.28; control group mean change=+3.22, 95% CI -0.87 to 7.31). Likewise there was a significant time by group interaction in 3 out

of 5 imputed datasets for subjective experience of fatigue (p=.007 to p=.026) and in 4 out of 5 imputed datasets for total fatigue severity (p=.000 to p=.017). No significant effects were found for fatigue impact (p=.550; imputed data sets non-significant).

As for physical activity related variables, patients in the intervention group presented significantly higher levels of leisure time physical activity (p= .000) and progress toward a personal physical activity goal (p=.000), also significant in all 5 imputed data sets (p=000 to p=0.21 and p=<.001, respectively). There was a significant increase in the intervention group from T1 to T2 for level of leisure-time physical activity (mean change=+79.11, 95% CI 39.71 to 118.52; control group mean change=-0.98, 95% CI -29.03 to 27.07), and personal physical activity goal progress (mean change=+2. 66, 95% CI 1.79 to 3.53; control group mean change= +0.20, 95% CI -0.66to 1.05). The interaction effect for the number of steps/day was of small magnitude and not significant (p=0.56; mean change=+448, 95% CI 33 to 861; control group mean change=-387, 95% CI -1096 to 322), significant in only one (out of five) imputed dataset (p=.027). There was a significantly higher proportion of physically active participants in the intervention group (26/35 - 74.3%) in comparison to the control group (11/33 - 33.3%; X^2=13.22, p= 0.00; RR=2.23 95% CI 1.32 to 3.75). Patients in either group reported no negative effects of exercise or participation in the study.

Repeated-measures ANCOVAs also showed a significant time by group interaction for physical and psychological HrQoL after controlling for the effect of the covariates (p=.002 and p=.047, respectively). Mean change in the intervention group from T1 to T2 was +5.11 (95% CI 1.05 to 9.17 and +5.28 (95% CI -0.39 to 10.17), respectively (control group mean change= -3.15, 95% CI -7.30 to 0.88 and -0.81, 95% CI -381 to 2.20). There was a significant interaction effect in 3 out of 5 datasets imputed for physical HrQoL (p=.000 to p=.006) and only in 2 out of 5 datasets for psychological HrQoL (p=.003 to p=.048). No significant effects were found for somatic symptoms (p=.456) and psychological distress (depression and anxiety: p=.671 and p=.276, respectively) with any of the approaches employed.

Discussion

This study examined the effect of a 12-weeks brief self-regulation (SR) based program for unexplained chronic fatigue (4-STEPS) targeting physical activity. Attrition to the trial was higher than initially anticipated (≥20%), but this study included a larger sample than what was established in the study protocol [23].

At post-treatment, there was a significant beneficial effect of the 4-STEPS program on the subjective experience of fatigue (primary outcome). Although the difference between the intervention and control conditions did not reach the 7 point target, the significant decrease in the subjective experience of fatigue in the intervention group (3.38) can be considered to be clinically significant as the difference exceeds 0.5 SD, a criterion used in other GET and CBT trials [42, 43]. Mixed-design analysis comparing the intervention and control conditions at T1 and T2 revealed a moderate beneficial effect of the 4-STEPS program on subjective experience of fatigue and total fatigue severity (g=0.44, g=0.39). These results are in line with the average effect size for fatigue severity found in a previous meta-analysis of graded exercise and psychological interventions for chronic fatigue management (g=0.41 and g=0.36) [10]. These effects are however lower than those found in other psychological-based minimal interventions [12, 15]. No significant differences were found between the proportion of patients in each condition who reached non-clinical levels of fatigue (<35) at T2; however the number of patients presenting non-clinical levels of fatigue in the intervention condition is comparable to what is reported in other trials [12, 13]. Furthermore, we found an increase in the number of patients in the intervention group presenting non-clinical levels of fatigue compared to baseline.

Beneficial effects were also found for leisure-time physical activity (g=0.77), resulting in a significantly higher number of active patients in the intervention group at T2. We observed a small increase in the daily number of steps in the intervention group (450 steps) as compared to a reduction in the daily steps in the control group, but time by group interaction was not statistically significant. Current guidelines of physical activity for individuals with chronic disease recommend a minimum of 6500-8500 steps

a day, which was achieved by the intervention group at post-treatment. Still, the average increase in the number of steps in pedometer-based interventions is about 2.215 steps/day (or effect size of 0.67), which is considerably higher than those obtained in our trial [44]. Earlier trials have found small to medium effects of exercise interventions on the levels of physical activity/capacity in chronic fatigue patients [42, 45]. Other studies did not find these beneficial effects [12, 46]. However, these studies measured physical activity in a different way, mainly in a laboratory setting making use of functional capacity measures [e.g. 46], walking tests [e.g. 42] or actigraphy [e.g. 12]. In addition, a large effect (g= 0.83) of the 4-STEPS program was found on patients' progress in the attainment of their personal physical activity goal. This result points at the important role of self-regulation cognitions and skills in self-set health behavior goal pursuit.

In addition, patients who received the 4-STEPS program showed a significant improvement in physical health-related quality of life (HrQoL; g=0.41). This effect is in line with the average effect size for functional impairment found in a previous meta-analysis (g=0.38) [10]. Furthermore, we found a significant effect of small magnitude for psychological HrQoL (p=0.47, g=0.33). These results point at the psychological deterioration and increasing disability resulting from the burden of a prolonged chronic condition. Likewise, no significant beneficial effects were found for psychological distress (depression and anxiety). This last result is in line with previous studies including CBT trials [10].

Because of contradictory findings of physical exercise programs in CF(S) it has been suggested recently that physical activity programs should incorporate flexible goals that take into consideration symptom fluctuation and rest [47]. In the present study, goals related to physical activities were personal and planned according to these principles. In addition, the findings of the present study support minimal contact interventions using manuals. As such, this theory-based brief intervention, using motivational interviewing principles and self-regulation skills training, encouraged patients to set self-chosen active and positive goals and provided them with the skills to put them into practice [16, 48].

In spite of its strengths, the present study also has some

limitations. First, the small sample size limits the generalizability of the findings. Likewise, the lack of significance found for some of the secondary outcomes may be due to low statistical power, as our study was not powered to detect changes in secondary outcomes. Second, this trial was carried out in health care centres and in patient associations. To deal with potential bias the randomisation procedure was stratified by sample, and repeated measure analyses were conducted controlling for the setting (Health care centres vs. Patient association). Differences in the recruitment strategy within these settings may have led to selection bias. Furthermore, the findings may also be biased by self-selection, due to the high rate of patients not interested in participating in the trial. It may be that patients willing to participate were more motivated to change than non-participants. Third, confirmation of CF(S) inclusion and exclusion criteria was based on self-reports according to the CDC criteria and it can therefore not be excluded that some patients did not fulfill all the criteria. Ideally, this diagnosis should also rule out other somatic and psychiatric causes of the symptoms, by means of a full clinical assessment and standardised psychiatric interview. Fourth, allocation of participants to the conditions was conducted prior to baseline assessments as the goal elicitation procedure took place at different moments for each condition (baseline assessment for the control group and at the second face-to-face session for the intervention group). This constitutes an additional potential source of bias. Fifth, the intervention was delivered by only one psychologist, which did not allow controlling for therapist effects in our analysis. Furthermore, due to resources constraints we could not assess treatment integrity, which is an important procedure to enhance validity of interventions. Sixth, men were largely underrepresented in the sample and as a consequence more studies are needed to determine the effectiveness of this program in men suffering from CF(S). Seventh, due to the fact that there are no normative data for the Portuguese CIS20, comparisons made regarding (non-)clinical levels of fatigue severity should be interpreted with care. Finally, this intervention combined motivational interviewing, several self-regulation techniques and motivational tools (e.g. pedometer) and the effect of these components cannot be separated. Future studies could address this

issue by using a full-factorial design.

In summary, this study shows that a brief SR intervention targeting (balanced) physical activity has significant post-treatment beneficial effects upon fatigue severity, physical activity, personal goal progress related to physical activity and health-related quality of life in chronic fatigue patients. This low-resource intervention looks promising for the management of chronic fatigue. A follow-up assessment (12-months) will provide the necessary information to evaluate the medium-term effects of the 4-STEPS program.

Other information

The trial is registered at http://www.controlled-trials.com, number ISRCTN70763996 and we have previously published the protocol of our trial [23]. This report followed the revised CONSORT guidelines for reporting randomized trials [49].

Acknowledgement

This study was partially funded by the Portuguese Foundation for Science and Technology with a grant to the first author (SFRH/BD/47579/2008). The authors would like to thank all patients that participated in this research, the directors and medical doctors from the Health care centres (USF Conde de Oeiras, USF São Julião, USF Marginal, USF Navegantes, Medicil), the volunteers from MYOS, Andreia Cordeiro and Maria João Gouveia. We thank Keegan Knittle for his help with the revision of the manuscript.

Informed Consent: All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (Portuguese Medical-Ethics Committe of the Regional Health Administration guidelines) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients before being included in the study.
Conflict of Interest: Marta Marques, Véronique de Gucht, Isabel Leal and Stan Maes, declare that they have no conflict of interest.

References

1. Fukuda K, Strauss S, Hickie I, Sharpe M, Dobbins J, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med. 1994;121:953-9.
2. Afari N, Buchwald D. Chronic Fatigue Syndrome: A review. Am J Psychiatry. 2003;160:221-36. doi: 10.1176/appi.ajp.160.2.221
3. Prins JB, Vand der Meer JWM, Bleijenberg G. Chronic fatigue syndrome. Lancet. 2006;367:346-55.
4. Clark L, White P. The role of deconditioning and therapeutic exercise in chronic fatigue syndrome (CFS). Journal of mental health. 2005;14(3):237-52. doi:10.1080/09638230500136308.
5. Fulcher K, White P. Strength and physiological response to exercise in patients with chronic fatigue syndrome. J Neurol Neurosurg Psychiatry. 2000;69:302-7. doi: 10.1136/jnnp.69.3.302.
6. Nijs J, Wallman K, Paul L. Chronic Fatigue Syndrome. In: Saxton JM, editor. Exercise and Chronic Disease: An Evidence-Based Approach. New York, USA: Routledge; 2011. pp. 322-338.
7. National Institute for Health and Clinical Excellence (NICE). Clinical guideline 53. Chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy: diagnosis and management of CFS/ME in adults and children. London; 2007.
8. Edmonds L, McGuire L, Price J. Exercise Therapy for Chronic Fatigue Syndrome. Cochrane Database Syst Rev. 2004;3:CD003200.
9. Price J, Mitchell E, Tidy E, Hunot V. Cognitive behaviour therapy for chronic fatigue syndrome in adults. Cochrane Database Syst Rev. 2008;3:CD001027.
10. Castell BD, Kazantsis N, Moss-Morris R. Cognitive Behavioral Therapy and Graded Exercise for Chronic Fatigue Syndrome: A Meta-Analysis. Clin Psychol Sci Pract. 2011; 18(4): 311-324. doi: 10.1111/j.1468-2850.2011.01262.x.
11. Malouff JM, Thorsteinsson EB, Rooke SE, Bhullar N, Schutte NS. Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: A meta-analysis. Clin Psychol Rev. 2008;28(5):736-45. doi:10.1016/j.cpr.2007.10.004.
12. Knoop H, Van der Meer J, Bleijenberg G. Guided self-instructions for people with chronic fatigue syndrome: a randomised controlled trial. Br J Psychiatry. 2008;190:340-1. doi: 10.1192/bjp.bp.108.051292.

13. Tummers M, Knoop H, van Dam A, Bleijenberg G. Implementing a minimal intervention for chronic fatigue syndrome in a mental health centre: a randomized controlled trial. Psychol Med. 2012;42(10):2205-15. doi: 10.1017/S0033291712000232.
14. Powell P, Bentall R, Nye F, Edwards R. Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. BMJ. 2001;322:387. doi:10.1136/bmj.322.7283.387.
15. Carver CS, & Scheier MF, (1998). *On the self-regulation of behavior*. New York. University Press.
16. Maes S, Karoly P. Self-regulation assessment and intervention in physical health and illness: a Review. Appl Psychol: Int Rev. 2005;54(29):267-99. doi:10.1111/j.1464-0597.2005.00210.x.
17. Michie S, Abraham C, Whittington C, McAteer J, Gupta S. Effective techniques in healthy eating and physical activity interventions: A meta-regression. Health Psychology. 2009;28(6):690-701. doi: 10.1037/a0016136.
18. Sniehotta FF, Scholz U, Schwarzer R. Bridging the intention–behaviour gap: Planning, self-efficacy, and action control in the adoption and maintenance of physical exercise. Psychology & Health. 2005;20(2):143-60. doi:10.1080/08870440512331317670.
19. Janssen V, Gucht V, Exel H, Maes S. A self-regulation lifestyle program for post-cardiac rehabilitation patients has long-term effects on exercise adherence. J Behav Med. 2013:1-14. doi:10.1007/s10865-012-9489-y.
20. Knittle K, Gucht V, Hurkmans E, et al. Targeting motivation and self-regulation to increase physical activity among patients with rheumatoid arthritis: a randomised controlled trial. Clinic Rheumat. 2013:1-8. doi:10.1007/s10067-013-2425-x.
21. Miller W & Rolnick S. Motivational interviewing: Helping people change. 3rd ed. NY: The Guiford Press; 2012.
22. Lundhal BW, Kunz C, Brownell C, Tollefson D, Burke BL. A meta-analysis of motivational interviewing: tewnty-five years of empirical studies. Res Social Work Prac. 2010;20(2):137-60. doi: 10.1177/1049731509347850.
23. Marques M, De Gucht V, Maes S, Leal I. Protocol for the "Four steps to control your fatigue (4-STEPS)" randomised controlled trial: A self-regulation based physical activity intervention for patients with unexplained Chronic Fatigue. BMC Public Health. 2012;12(202). doi:10.1186/1471-2458-12-202

24. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 8 ed. Baltimore: Lippincott Williams & Williams; 2009.
25. Wagner D, Nisenbaum R, Heim C, Jones JF, Unger ER, Reeves WC. Psychometric properties of the CDC symptom inventory for assessment of chronic fatigue syndrome. Pop Health Metrics. 2005;3:8. doi:10.1186/1478-7954-3-8.
26. Marques M De Gucht V, Gouveia MJ, Cordeiro A, Maes S. Psychometric properties of the Portuguese version of the Checklist of Individual Strength (CIS20-P). Psych, Commun & Health. 2013;22(1):11-8. doi:10.5964/pch.v2i1.57.
27. Vercoulen J, Alberets M, Bleijenberg G. De Checklist Individual Strenght (CIS). Gedragstherapie. 1999;32:31-6.
28. De Vree B, van der Werf S, Prins J, Bazlmans E, Vercoulen J, Servaes P. Meetinstrumenten bij chronische vermoeidheid. Gedragstherapie. 2002;35:157-64.
29. Cleeland C, Ryan K. Pain assessment: global use of the brief pain inventory. Ann Acad Med Singapore. 1994;23:129-38.
30. Wendel-Vos G, Schuit A, Saris W, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56:1163-9. doi.10.1016/S0895-4356(03)00220-8.
31. Ainsworth B, Haskell W, Whitt M, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc. 2000;32(Suppl 9):498-504.
32. Ainsworth B, Haskell W, Herrmann S, et al. Compendium of Physical Activities: A second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575-81. doi: 10.1249/MSS.0b013e31821ece12.
33. Welk GJ, Differding JA, Thompson RW, Blair SN, Dziura J, Hart P. The utility of the Digi-walker step counter to assess daily physical activity patterns. Med Sci Sports Exerc. 2000;32(9 Suppl):S481-8.
34. Le Masurier GC, Tudor-Locke C. Comparison of pedometer and accelerometer accuracy under controlled conditions. Med Sci Sports Exerc. 2003;35(5):867-71. doi: 10.1249/01.MSS.0000064996.63632.10
35. Maes S, Karoly P, De Gucht V, Ruehlman LS, Heiser W: The self-regulation skills battery (SRSB). Leiden(NL)/Phoenix (AZ): Leiden University & Arizona State University; 2006.
36. Ware JE, Kosinski M, Turner-Bowker DM, Gandek B: How to score

version 2 of the SF-12® Health Survey. Lincoln, RI: Quality Metric Incorporated; 2002.
37. Kroenke K, Spitzer R, Williams J. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med. 2002;64:258-66.
38. Degoratis L. Brief Symptom Inventory: Administration, Scoring and Procedures Manual. 4 ed, Minneapolis: National Computer System; 1993.
39. Faul F, Erdfelder E, Lang A, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioural and biomedical sciences. Behav Res Methods. 2007;39:175-91. doi: 10.3758/BF03193146.
40. Stulemeijer M, de Jong L, Fiselier T, Hoogveld S, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ. 2005;330(7495):820. doi 10.1136/bmj.38301.587106.63.
41. Hedges LV. Distribution Theory for Glass's Estimator of Effect size and Related Estimators. J Educ Behav Stat. 1981;6(2):107-28.
42. White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. The Lancet. 2011;377(9768):823-36. doi:10.1016/S0140-6736(11)60096-2.
43. Vos-Vromans DC, Smeets RJ, Rijnders LJ, et al. Cognitive behavioural therapy versus multidisciplinary rehabilitation treatment for patients with chronic fatigue syndrome: study protocol for a randomised controlled trial (FatiGo). Trials. 2012;13(1):71. doi:10.1186/1745-6215-13-71.
44. Tudor-Locke C, Craig CL, Aoyagi Y, et al. How many steps/day are enough? For older adults and special populations. Int J Behav Nutr Phys Act. 2011;8(1):80. doi:10.1186/1479-5868-8-80.
45. Wallman K, Morton A, Goodman C, Grove R, Guilfoyle A. Randomised controlled trial of graded exercise in chronic fatigue syndrome. Med J Aust. 2004;180(9):444-8.
46. Moss-Morris R, Sharon C, Tobin R, Baldi J. A randomized controlled graded exercise trail for chronic fatigue syndrome: outcomes and mechanisms of change. J Heal Psychol. 2005;10(2):245-59. doi:10.1177/1359105305049774.

47. Nijs J, Paul L, Wallman K. Chronic fatigue syndrome: an approach combining self-management with graded exercise to avoid exacerbations. J Rehabil Med. 2008;40:241-7. doi: 10.2340/16501977-0185.
48. De Gucht V, Maes S. Explaining medically unexplained symptoms: toward a multidimensional theory-based approach to somatisation. J Psychosom Res. 2006;60:349-35. doi:10.1016/j.jpsychores.2006.01.021.
49. Schulz K, Altman D, Moher D, and the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010; 8(1):18. doi: 10.1136/bmj.c332.

Figure 1 Flow diagram of participants through the intervention.

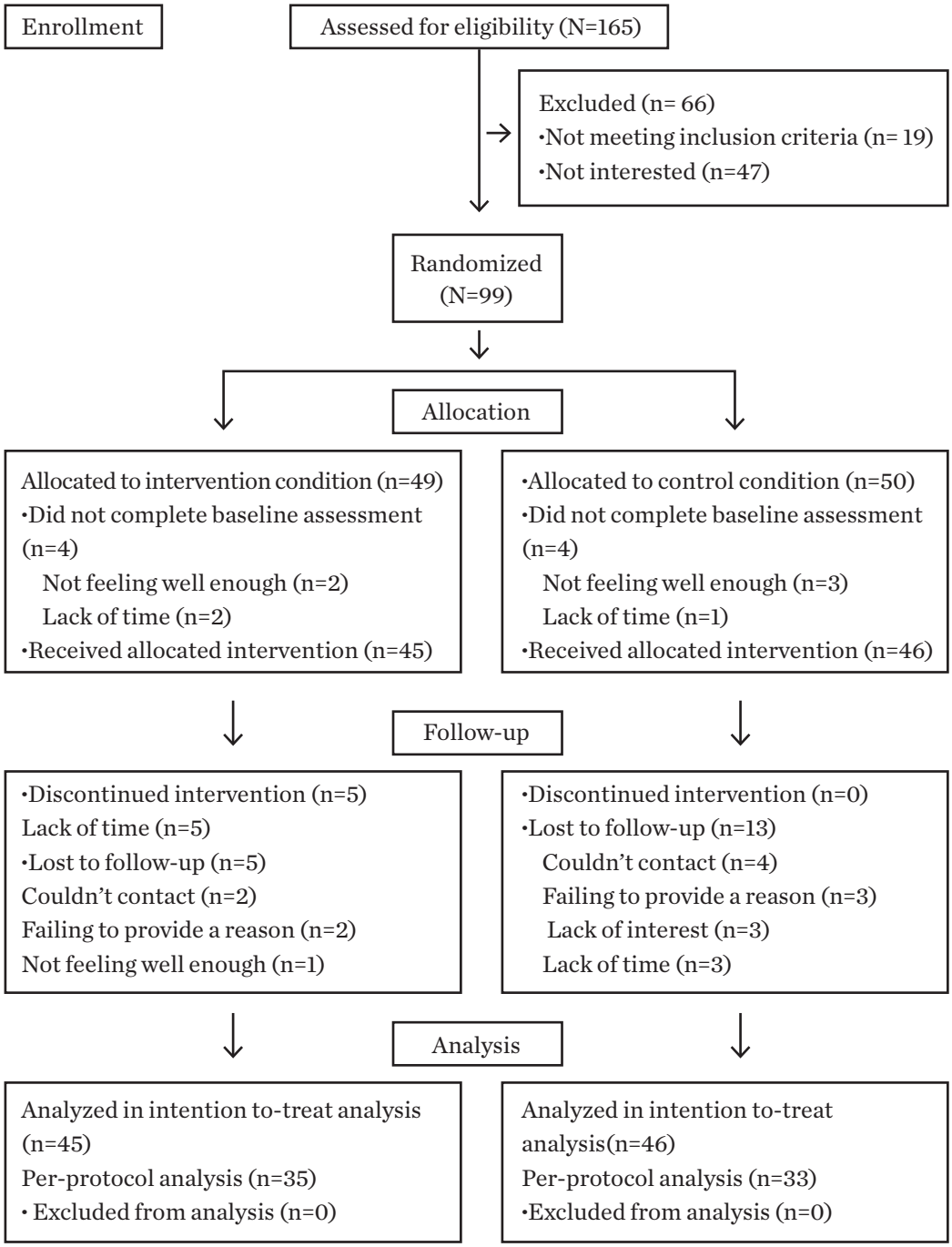


Table 1 Baseline demographics and patient characteristics

Characteristic	**Intervention** (n=45)	**Control** (n=46)	***p***
Age	46.96±10.39	49.20±11.49	0.33
Gender (women)	44 (97.8)	45 (97.8)	1.00
Education			
Primary	12 (26.7)	16 (34.8)	
Secondary	17 (37.8)	17 (37.0)	0.65
Higher	16 (35.6)	13 (28.3)	
Employed	24 (54.3)	25 (54.3)	1.00
Not working due to fatigue [1]	10 (45.5)	11 (47.8)	1.00
Abseentism (n. days) [2]	6.20 ± 10.44	14.36 ± 22.61	0.14
Physically active[3]	15 (33.3)	17 (37)	0.82
Disease duration (years)	9.81 ± 8.02	10.96 ± 9.06	0.53
Number of medical consultations	4.03± 2.88	5.10 ± 4.43	0.20
Number of major CDC CFS symptoms	6.42 ± 1.29	6.70 ± 1.38	0.33
Diagnostic criteria			
ICF	5 (11.1)	3 (6.5)	0.49
CFS	40 (88.9)	43 (93.5)	
Clinical Levels of Fatigue[4,5]			
Yes	42 (93.3)	43 (93.5)	1.00
No	3 (6.7)	3 (6.5)	
Setting			1.00
Health Care Centres	24 (53.3)	25 (54.3)	
Patient Association	21 (46.7)	21 (45.7)	

Note. Values are presented as Mean ± Standard Deviation or Frequencies (%). [1] n=21 in each condition. [2] n=20 (Intervention condition); n=22 (Control condition). [3]Results for completers [Physically active: Intervention group = 14/35 (40%); Control condition= 15/33 (45.5%); p= 0.65]. [4]Cut-off score of 35 on the Subjective Fatigue sub-scale of the CIS20. [5]Results for completers [clinical levels= 34/35 (97.1%) and 30/33 (90.9%); p=0.35]. CDC = Centres for Disease Control and Prevention; ICF = Idiopathic Chronic Fatigue; CFS = Chronic Fatigue Syndrome.

Table 2 Changes in outcomes between baseline (T1) and post-treatment (T2)

	Intervention (n=45)		**Control** (n=46)		**Group x Time interaction[a]**		
Outcome	**T1**	**T2**	**T1**	**T2**	**F**	***p***	***g*[b]**
Subjective fatigue	46.00±6.30	42.62±9.93	47.00±7.66	47.35±8.31	F=4.965	.028	0.44
Fatigue severity[1]	98.40±16.43	93.73±22.37	103.54± 19.07	106.76 ± 20.32	F=5.721	.019	0.39
Fatigue impact	6.25±1.89	5.89±2.38	6.88±1.90	6.33±2.21	F=0.360	.550	0.09
Leisure-time PA[2]	41.56±70.59	120.67±146.19	58.37 ±106.28	57.39± 152.00	F=20.38	.000	0.77
PA (steps/day)	6629±2716	7077±2746	6773±2820	6385±2830	F=3.748	.056	0.30
Goal progress	1.50±2.39	4.16±3.30	2.32±3.04	2.51±2.84	F=16.37	.000	0.83
Physical HRQoL	38.22±17.78	43.33±21.87	31.30±18.90	28.15±21.43	F=9.880	.002	0.41
Mental HRQoL	41.57± 16.12	46.85±19.71	37.59 ±17.62	36.79±19.15	F=4.075	.047	0.33
Somatic distress	14.02±4.04	13.05±4.72	16.20 ±4.47	15.76±4.48	F=0.562	.456	0.12
Depression	1.49±0.88	1.55±0.95	1.55±0.95	1.91±0.93	F=0.182	.671	0.05
Anxiety	1.63±0.77	1.44±0.79	1.66±0.79	1.64±0.81	F=1.203	.276	0.29

Note. Values are presented as mean ± standard deviation. [a] Mixed design repeated measures using intention to treat analysis, adjusted for disease duration and setting (Health care centres vs. Patient association). [b]g = Hedge's g (interpreted according to Cohen's d (0.20- small; 0.50- medium; 0.80- large). [1]CIS20 total score. [2] Descriptives are presented in raw form. PA= physical activity. HRQoL= Health-related quality of life.

Table 3 Comparison between methods of data analysis (Complete Dataset, Last-Observation Carried Forward, Multiple Imputation)

Outcome	*F*[a]	*p*	*g*[b]	Model
Subjective Fatigue	4.97	.028	0.44	LOCF
	4.49	.038	0.55	Complete Case
	7.75	.007	0.58	Smallest MI effect (3/5 sig)
Fatigue severity[1]	5.72	.019	0.39	LOCF
	5.43	.023	0.51	Complete Case
	13.51	.000	0.69	Smallest MI effect (4/5 sig)
Fatigue Impact	0.36	.550	0.09	LOCF
	0.56	.457	0.15	Complete Case
	1.20	.331	0.12	Smallest MI effect (0/5 sig)
Leisure-time PA	20.38	.000	0.77	LOCF
	11.19	.001	0.71	Complete Case
	13.44	.000	0.70	Smallest MI effect (5/5 sig)
PA (Steps/day)	3.75	.056	0.30	LOCF
	3.82	.055	0.40	Complete Case
	5.04	.027	0.43	Smallest MI effect (1/5 sig)
PA Goal Progress	16.37	.000	0.83	LOCF
	16.83	.000	1.04	Complete Case
	22.84	.000	1.18	Smallest MI effect (5/5 sig)
Physical HRQoL	9.88	.002	0.41	LOCF
	9.89	.003	0.52	Complete Case
	14.46	.000	0.57	Smallest MI effect (3/5 sig)
Mental HRQoL	4.08	.047	0.33	LOCF
	3.91	.052	0.43	Complete Case
	9.07	.003	0.57	Smallest MI effect (2/5 sig)
Somatic Distress	0.56	.456	0.12	LOCF
	0.42	.521	0.15	Complete Case
	1.79	.152	0.26	Smallest MI effect (0/5 sig)
Depression	0.18	.671	0.05	LOCF
	0.21	.646	-0.07	Complete Case
	0.83	.210	0.02	Smallest MI effect (0/5 sig)
Anxiety	1.20	.276	0.29	LOCF
	1.02	.317	0.28	Complete Case
	5.06	.027	0.51	Smallest MI effect (1/5 sig)

[a] Mixed design repeated measures, adjusted for disease duration and setting (Health care centres vs. Patient association). [b]g = Hedge's g [1]CIS20 total score. PA= physical activity. HRQoL= Health-related quality of life. LOCF = Last-observation-carried-forward. MI= Multiple Imputation.

07

Physical activity goal progress and self-regulation skills mediate medium-term effects of a self-regulation based physical activity program for chronic fatigue

Manuscript under revision
M. Marques, V. De Gucht, I. Leal & S. Maes (XXXX). Physical activity goal progress and self-regulation skills mediate long-term effects of a self-regulation based physical activity program for chronic fatigue.

Abstract

Background: Physical activity is considered to be beneficial for patients suffering from unexplained chronic fatigue.
Purpose: Examine the medium-term effects of a brief physical activity (PA) self-regulation (SR) based intervention (4-STEPS program), and explore the mediating effects of PA and SR skills.
Methods: A two-arm randomized controlled study (Usual Care vs 4-STEPS) was carried out. The 4-STEPS program consisted of Motivational Interviewing and SR-skills training. Fatigue severity (primary outcome) and impact, PA, health-related quality of life (HrQoL), somatic and psychological distress were assessed at baseline, post-treatment (12 weeks) and 12 months follow-up.
Results: Ninety-one patients (45 intervention and 46 controls) were included. At follow-up, there were significant treatment effects on fatigue severity (g=0.72) and fatigue impact, leisure-time PA, and physical and psychological HrQoL. Fatigue severity at follow-up was partially mediated by post-treatment progress on a personal PA goal and SR skills (effect ratio= 26% and 32%).
Conclusions: Results suggest that a brief intervention, focusing on the formulation and pursuit of personal PA goals and the use of SR skills, produces sustained benefits for fatigue severity.

Trial Registration: ISRCTN70763996

Keywords*:* chronic fatigue, randomized controlled trial, physical activity, self-regulation, skills, goals.

Introduction

Fatigue is a common symptom, usually transitory and explained by life circumstances, but for some, fatigue is medically unexplained and severe, resulting in disability and lower health-related quality of life [1, 2]. Unexplained fatigue is considered to be chronic if it lasts for at least 6 months (i.e. idiopathic chronic fatigue-ICF). If additional somatic symptoms as defined by the Centres for Disease Control and Prevention (CDC) are present, it is classified as Chronic Fatigue Syndrome (CFS) [3].

Prolonged physical inactivity (rest) and decreased physical capacity are considered to be perpetuating factors in CF(S) [4-6]. At the same time, high levels of physical activity can cause overexertion and perpetuate fatigue symptoms [7, 8]. Not surprisingly, it is common to find a "boom-and-bust pattern" in these patients, which is the systematic alternation between periods of over-activity (when feeling good) and, as a consequence of that, feeling extremely fatigued and having to rest for longer periods of time [9, 10]. It is therefore recommended that CF(S) patients engage in physical activity based on Graded Exercise Therapy (GET) [1, 11].

GET consists of exercise prescription (aerobic activities) adapted to the patient's physical capacity. GET aims to gradually increase exercise at a level that does not exacerbate symptoms. Patients are advised not to exceed the recommended levels of physical activity (in order to avoid overexertion) and are encouraged to maintain these levels even if symptoms get worse. GET has been shown to have beneficial effects on chronic fatigue management [12-14]. Because of the benefits of physical activity in patients suffering from CF(S), many Cognitive Behavioural Therapy (CBT) trials have also incorporated a graded exercise component. CBT also has beneficial effects on chronic fatigue [12, 13, 15]. Despite the beneficial effect of both GET and CBT on CF(S) patients, effects of trials are of small magnitude and heterogeneous [12,13]. Some trials found limited effects of these interventions [e.g. 16, 17], while others proved to be very effective [e.g. 18, 19]. One explanation for the differences in effectiveness may be that some interventions result in creating cognitive or behavioural changes that may mediate the

effect of the intervention on fatigue, while others do not result in such changes. In the present article we will therefore not only report on the medium-term effects of a self-regulation physical activity based program for CF(S) patients, but we will also explore possible mediators of these effects, more specifically physical activity and self-regulation skills.

Recent studies have shown that self-regulation (SR) based interventions are effective in promoting long-lasting health behaviour change in various patients suffering from chronic diseases [20-22]. SR is one of the most prominent perspectives on health behaviour change, and considers that behaviour is a goal driven process [23, 24]. This dynamic-goal process consists of a goal selection and goal setting phase, an active goal pursuit or action phase and a goal attainment or maintenance phase, in which motivational and volitional aspects interact. Several SR cognitions and skills are guiding this process, such as self-efficacy, personal goal-setting, planning, self-monitoring, feedback, emotional and attention regulation and relapse prevention [23]. Personal goal setting, a central aspect in SR theory, is a first step and implies that formulating self-chosen and personally important goals guide behavior change and increase the likelihood of goal achievement and maintenance [23-25].

Motivational interviewing (MI), a "collaborative conversation style for strengthening a person's own motivation and commitment to change" ([26] p. 12) is frequently used to evoke and strengthen patients' own motivation and confidence to change, and to support patients in setting personal health-related goals by increasing the personal relevance of health goals. MI is considered especially helpful in helping patients move from ambivalence towards behavior change [26]. While MI mainly focuses on SR cognitions, SR skills play an important part not only in the formulation of health-related goals (e.g. physical activity) but also during active goal pursuit and during the maintenance phase of the behavioral change process [23]. Recent meta-analyses showed that interventions employing a combination of SR-skills (including self-monitoring) were more effective than interventions not using these techniques in increasing PA in the general population [27] and in improving chronic disease related outcomes [28].

Based on the self-regulation cognitions and skills described above we developed a brief SR-intervention targeting physical activity for patients with CF(S) (the "4-STEPS to control your fatigue" program). The 4-STEPS program consists of a combination of MI sessions, telephone self-regulation counseling, and SR skills based patient manuals. In this program participants set their own physical activity goals and are advised to gradually increase their physical activity levels according to a specific personal scheme [29], allowing flexibility in the intensity and duration of exercise according to symptom fluctuation, without exceeding one's own capacity. This also implies that physical activity can be reduced or even stopped when symptoms get worse [29-31]. Furthermore, balance between activity and rest is also taken into account.

The 4-STEPS program was tested in a randomized controlled trial [32], in which patients were either assigned to the control group (usual care) or to a 12-week self-regulation intervention (4-STEPS program). Post-treatment beneficial effects of the 4-STEPS program were found for fatigue severity, health-related quality of life, leisure-time physical activity and perceived physical activity goal progress. No effects were found for fatigue impact on daily life, daily steps, somatic distress, and psychological distress (depression and anxiety) [33].

The first objective of the present study is to report the 12-months follow-up results of the 4-STEPS intervention on fatigue severity (subjective experience and fatigue severity) and impact on daily life, physical activity (leisure-time physical activity and daily steps), health-related quality of life (physical and psychological component), somatic distress and psychological distress (anxiety and depression). The second objective is to examine the mediators of intervention effects on the subjective experience of fatigue. It is hypothesized that the intervention increases the intermediate targets of our intervention – physical activity and the use of self-regulation skills -, and that this increase mediates the medium-term effects of the intervention on fatigue improvement.

Method

Trial design

This study concerns the follow-up results of a randomized controlled trial that has been previously described in full detail [32]. It was a two-arm 12-week multicentre randomized controlled trial. Randomisation was stratified by sample (Health care centre and Patient Association), and within the first sample also by centre, with equal randomisation (1:1) to either the intervention condition (4-STEPS program) or the control condition. Allocation sequence was based on computer-generated allocation numbers carried out by a member of the research team, who did not take part in the subsequent phases of the trial. Group allocation was known to participants, therapist and outcome assessors. Patients were assessed at baseline (T1), and 3 (post-treatment-T2) and 12 months (follow-up- T3) thereafter. Approval was obtained from the Portuguese Medical-Ethics Committee of the North Regional Health Administration and from the board of each participating health care center. The trial was conducted between January 2011 and December 2012.

Participants and procedure

Adult patients meeting the CDC criteria for idiopathic chronic fatigue (i.e. presenting a main complaint of unexplained fatigue of at least six months duration) were eligible to participate in the study [3]. Additional inclusion criteria were to fully understand and speak Portuguese and to have the capacity to provide informed consent. Patients presenting a concurrent somatic condition and/or a severe psychiatric disorder that could explain fatigue symptoms (according to the CDC criteria for exclusionary medical and psychiatric conditions [3]) were excluded.

The trial was conducted in (a) several Portuguese Health Care Centres (public primary care centres and one private practice) and (b) via the Portuguese Fibromyalgia and Chronic Fatigue Syndrome Patient Association. In the first case, physicians referred patients based on the inclusion/ exclusion criteria. Patients from the patient association who met the criteria (i.e. clinical diagnosis of unexplained chronic fatigue) and indicated their willingness

to participate in the study received a letter from the association containing a description of the trial. All participants were informed of the content and structure of the trial and invited for the baseline assessment in the health care centre or at the office of the patient association. Patients willing to participate signed a written informed consent before enrolment. Baseline assessment consisted of a structured interview with each patient in which self-reported questionnaires were completed. The research team checked inclusion and exclusion criteria, using self-report measures based on the CDC criteria. A similar procedure was used for the assessments at T2 and T3.

Intervention

Participants continued to receive their usual care. Patients assigned to the control condition received a flyer with information about the general health benefits of physical activity and current physical activity guidelines for adults [34]. In addition, they set a personal physical activity goal for the upcoming months. Participants assigned to the intervention condition additionally received the "4-STEPS to control your fatigue" program.

One health psychologist (with expertise in motivational interviewing) delivered the "4-STEPS" program to individual patients. The intervention was based on the self-regulation phases of goal pursuit (goal selection and setting, active goal pursuit and goal attainment, maintenance and disengagement) [23]. First, participants received two 1-hour face-to-face individual motivational interviewing sessions (weeks 1 and 3) aimed at: (a) exploring important health and life goals, to which a physical activity goal could be related, (b) reducing ambivalence towards change (c) increasing participants' motivation and confidence to be physically active and (c) setting a specific personal physical activity goal. This personal physical activity goal, which took into consideration the graded activity principles of flexibility and balance, developed by Nijs and colleagues [29] was set by each patient during the second MI session. Patients also formed action plans regarding their goal (i.e. which physical activities would be done, and when, where, for how long and with whom each would take place).

Second, participants received a booklet containing information regarding: (a) the diagnosis of CF(S), (b) the factors contributing to a better or worse prognosis, and (c) the link between CF(S) symptoms and physical (in-)activity and the boom-bust pattern (i.e. erratic pattern of rest and activity).

Third, a self-regulation based workbook was given to the patients. The self-regulation workbook was divided in four steps, each one focusing on specific self-regulation cognitions and skills: Step 1-"Am I ready to start?" (focusing on self-efficacy, motivation, and control over competing goals), Step 2- "My physical activity goal" (focusing on goal-setting, action planning and self-monitoring), Step 3 "Overcoming obstacles" (focusing on coping efficacy and planning, feedback, attention and emotion regulation (i.e. control of distracting stimuli and negative emotions to maintain a focus on goal pursuit) and Step 4 "I am physically active...and I want to keep it this way" (focusing on relapse prevention, including coping efficacy and planning and goal reformulation).

Fourth, patients received two brief self-regulation based telephone-counseling sessions (weeks 5 and 9). This telephone support aimed at reviewing the participants' physical activity goal and providing relapse prevention strategies.

Fifth, patients received a pedometer to register their physical activity levels on a daily basis (steps taken) during the intervention period. In addition, at the end of the first MI session, patients received a weekly daily activities record to fill in, between sessions, with the amount of time each day spent in physical activities, mental activities and rest. This provides information on activity fluctuation throughout the week (possible erratic rest and activity pattern) and how to best include PA in the daily schedule. The first record was used to facilitate goal setting at the second MI session. After that, patients received several records that they could use to self-monitor daily activity patterns, if they would like to do so.

Finally, patients received a leaflet for their partner or significant other with relevant information on chronic fatigue, the objective of which was to increase social support.

Outcomes

Patient characteristics Socio-demographic characteristics included age, gender, education and employment status (Table 1). Clinical information was gathered using the following indicators: (1) presence of persistent fatigue, (2) duration of fatigue symptoms, (3) impact of fatigue on daily activities (4) whether fatigue was alleviated by rest, (5) number of medical consultations, and (6) a CDC based symptom checklist for CFS [35]. The checklist presents 19 major and minor symptoms of CFS as defined by the CDC criteria [3]. Respondents were asked to indicate if they experienced each of the symptoms during the last 6 months. For the purpose of this study a dichotomous scale (Yes/No) was used. A total symptom score was calculated by adding up the number of major symptoms presented (ranging from 1 to 8). To be diagnosed with CFS, patients need to have a complaint of persistent unexplained fatigue (at least 6 months) that leads to a significant disability and to have at least 4 of the major CFS symptoms listed by the CDC. Patients not fulfilling the full criteria were classified as ICF patients. The self-reported measures also included a question regarding the presence of chronic disease and/or psychiatric disease, as well as name and duration, if any.

Fatigue was assessed using the Checklist of Individual Strength (CIS20-P) [36], a well-validated and reliable measure for assessing fatigue severity in chronic fatigue patients [37]{Vercoulen, 1999, De Checklist Individual Strenght (CIS);Marques M, , Psychometric properties of the Portuguese version of the Checklist of Individual Strength (CIS20-P)}. The CIS20-P is a 20 item self-report measure that assesses four dimensions of fatigue: *subjective experience of fatigue*, *concentration*, *motivation* and *daily activities*. Items are rated on a 7-point scale. Total score of fatigue severity is calculated by adding up the scores from each dimension. For the purpose of this study only the subjective experience of fatigue dimension (primary outcome) and the total fatigue severity score were used. A cut-off point of 35 on the subjective experience of fatigue dimension of CIS20-P (range: 8-56) is usually used to define a clinical level of fatigue [38].

Fatigue impact was measured by means of a modified version of the pain interference dimension of the well validated Brief Pain

Inventory (BPI) consisting of 7 items [39]. Participants were asked to rate on a 10-point scale how their fatigue interfered with several aspects of their life. Total score was used as the outcome, ranging from 0 to 10. Higher scores indicate a higher impact of fatigue.

Physical activity was assessed by means of:

(a) A self-report measure of *leisure-time physical activity* based on the Short Questionnaire to Assess Health-enhancing Physical Activity (SQUASH) [40]. Participants indicate the number of days per week and minutes per day in which they engage in physical activities (bicycling, walking and other activities such as swimming). For each activity of at least moderate intensity (≥3 METs based on the categories of the Ainsworth's compendium of physical activities [41, 42], total minutes of physical activity per week are calculated by multiplying frequency (days/week) and duration (minutes/day). Total minutes of leisure-time physical activity (moderate to vigorous physical activity - MVPA) per week are calculated by taking the sum of each activity score.

(b) Physical activity was also measured by means of a *pedometer*. Daily steps were assessed using Yamax Digiwalker SW-200 pedometers, which proved to be accurate and reliable [43, 44]. Participants were asked to wear the pedometer for seven consecutive days and register the daily number of steps at the end of each day. The mean of the daily steps over these seven days was used as an outcome measure.

(c) Physical activity goal progress and achievement was assessed at T1 and T2. Using a standardized goal-elicitation procedure, respondents specified at baseline a personal physical activity goal that they wished to pursue over the next months. At post-treatment, respondents were reminded of their personal goal and asked to indicate their progress on a 10 cm visual analogue scale (VAS), ranging from "I haven't started yet" (0) to "I have achieved my goal" (10) [45].

Health-Related Quality of Life *(HRQoL)* was measured using the Short Form Health Survey-12 (SF-12V.2) [46]. The SF-12v2 is a well-validated measure that allows to calculate a physical functioning score (Physical HRQoL) and a psychological functioning score (Psychological HRQoL), ranging from 0 to 100, with lower scores representing worse HRQoL.

Somatic distress was assessed with the Patient Health Questionnaire-15 (PHQ-15), which measures the presence and severity of 15 somatic symptoms (e.g. back pain), scored on a 0-3 scale. Higher scores indicate higher somatic symptom severity (range: 0-30) [47].

Psychological distress was assessed using the Depression and Anxiety subscales from the well-validated and widely used Brief Symptom Inventory (BSI) [48]. Individuals rank each symptom on a 5-point scale, with higher scores representing more psychological distress. Scores were calculated by taking the mean of the items of each subscale (range: 0-4).

Self-regulation skills were measured at T2 using the Self-Regulation Skills Battery (SRSB) [45], which assesses the extent to which participants use self-regulation skills in pursuing a previously stated personal physical activity goal. We assessed six self-regulation skills (18 items): planning, self-monitoring, seeking feedback, focus attention on goal pursuit, emotional regulation, coping with problems and goal persistence. A composite score was calculated by taking the average of the mean scores of each subscale (range 1-5). The internal consistency of the total scale was very high (Cronbach's alpha=0.95).

Outcomes were assessed at baseline (T1), post-treatment (T2) and follow-up (T3). The T2 measures of perceived physical activity goal progress and self-regulation skills were used as mediators.

Sample size

An a priori analysis [49] using an independent sample t-test (5% significance level) showed that a sample of 34 participants in each group would have 80% power to detect a mean difference of 7 points [50, 51] on the subjective experience of fatigue dimension of the CIS20-P between the intervention and the control group. Anticipating a possible dropout of 20% we aimed at recruiting 41 subjects per group.

Statistical Analyses

Descriptive analyses were performed for gender, age, education, employment, clinical information and use of health care resources. Differences between groups at T1 were analyzed using t-tests

(for continuous variables) and univariate chi-square tests (for dichotomous variables). At T3, an independent samples t-test was conducted to assess the difference in subjective experience of fatigue between the intervention group and the control group (primary outcome). The effects of the intervention on the proposed outcomes were examined using a 3 (timeline: T1, T2 and T3) x 2 (condition: control and intervention) mixed-model repeated measures analysis of covariance (ANCOVA), controlling for setting (Health care centres vs. Patient association) and disease duration. Whenever there was a significant time x group interaction, contrasts were tested for significance. We calculated effect sizes for contrasts, which were the standardized mean differences with Hedge's *g* correction for small samples [52], interpreted according to Cohen's guidelines (values of 0.20, 0.50 and 0.80 correspond to small, medium and large effect sizes). Prior to the analyses, data was inspected for normality and homogeneity of variance. Leisure-time physical activity was not normally distributed at any of the time points and a logarithmic transformation was carried out for further analyses. Assumption of sphericity was checked using Mauchly's test. Whenever this assumption was violated, the *Greenhouse-Geisser* correction was applied. Data was analysed with intention-to-treat analyses (ITT) using the last-observation-carried-forward method (LOCF), which included all participants for whom complete baseline data was available. We undertook sensitivity analyses to test the robustness of the results of the mixed design ANCOVAs by repeating all analyses with completers only, and no significant differences were found between the two approaches. For this reason, main results report the ITT analysis. Missing values at baseline (incomplete assessment on daily steps and goal progress) were imputed using Multiple Imputation. Additional chi-square analyses were conducted for the complete dataset to compare the number of patients in each group who a) did not meet non-clinical levels of fatigue severity (<35) assessed by the subjective experience of fatigue dimension of the CIS20-P, and b) who were physically active. Effect sizes were Risk Ratio´s (RR).

To test mediation, we conducted a bootstrapping procedure developed by Preacher and Hayes [53], using the PROCESS macro for SPSS. We used simple mediation models, in which separate

analyses were conducted to test the indirect effect of treatment condition (independent variable) on changes in subjective experience of fatigue at follow-up (dependent variable) through the putative mediators: 1) daily steps taken (a more objective physical activity measure), 2) perceived physical activity goal progress, and 3) use of self-regulation skills. The mediator is assumed to be significant at $p<0.05$ if the corresponding 95% confidence interval (CI) for the indirect effect does not include zero. In addition, when there were significant indirect effects, the ratio of the indirect effect to the total effect was calculated to express the strength of the mediation effects (i.e. the amount of the total effect that is explained by the indirect effect via the mediator). We used a resample procedure of 5000 bootstrap samples (bias corrected), controlling for setting (Health care centres vs. Patient association) and disease duration. Data analyses were conducted using the statistical software SPSS v22.

Results

Participant flow and patient characteristics

The flow of patients through the trial and reasons for exclusions and withdrawals are shown in Figure 1. A total of 165 individuals were identified as eligible to participate and were informed about the study. Of these, 91 patients randomly allocated to either the 4-STEPS program or the control condition completed baseline assessment and received allocated treatment (n=45 and n=46, respectively). Sixteen (35%) participants in the intervention group and fifteen (32%) participants in the control group were lost to follow-up.

Demographics and clinical characteristics are presented in Table 1. No significant differences were found for demographics and clinical variables between the intervention and the control group at T1.

Intervention effects

At T3, there was a significant difference of 6.57 points in subjective experience of fatigue between the intervention and the control

group (t=-3.58, p=0.01 95% CI -10.3 to -2.80, g=0.72). There was a near-significant difference in the number of patients presenting non-clinical levels of fatigue between the intervention (7/29-24.1%) and control group (2/31-6.5%; X^2=3.68, p=.076, RR= 3.74, 95% CI 0.85 to 16.52). Mixed-design repeated measures analyses of covariance (ANCOVA) revealed a significant time by group effect for subjective experience of fatigue (p=.003) and total fatigue severity (p=.003), after controlling for the effect of the covariates (Table 2). In both analyses, contrasts revealed that significant changes occurred between T1 and T3 (p=.004, g= 0.66 and p=.005, g= 0.54, respectively). In the intervention group there was a significant decrease from T1 to T3 in the subjective experience of fatigue (- 4.04; mean change control group = +1.52) as well as in total fatigue severity (mean change intervention group= -5.98; mean change control group = +4.85). In addition, there was a significant effect of the intervention on fatigue impact (p=.018). Contrasts revealed a significant time by group interaction when comparing impact of fatigue between T2 and T3 (p=.003, g= 0.39).

Regarding physical activity there was a significant time by group interaction for level of leisure-time physical activity (p=.011). Statistical contrasts revealed that changes were significant from T1 to T3 (p=.012, g= 0.21). No significant group x time interaction was found for number of daily steps taken (p=.151). Furthermore, there was a significantly higher number of physically active participants in the intervention group (19/29 – 65.9%) in comparison to the control group (11/31 – 35.5 %; X^2= 5.41, p=.020; RR=1.84, 95% CI 1.07 to 2.21) at T3.

There was a significant time by group effect for both physical and psychological HrQoL (p=.002). Contrasts revealed that changes were significant from T1 to T3 (p=.002, g=0.39 and p=.004, g=057, respectively). In the intervention group there was a significant increase from T1 to T3 in physical HrQoL (+4.55; vs. mean change control group = -3.03) and psychological HrQoL (+8.82; vs. mean change control group = -1.32).

No significant time x group effects were found for somatic symptoms (p=.624), depression (p=.605) and anxiety (p=.365).

Mediation analysis

Table 3 shows the results of the mediation analysis for each proposed mediator. Mediation tests showed that daily steps at T2 (objective measure of physical activity) did not mediate the effects of treatment on fatigue severity at T3 (95% CI -1.92 to 1.49). By contrast, physical activity goal progress for which a significant time by group effect was found at T2 (F=16.37, p=.000, g=0.83), partially mediated the effect of the 4-STEPS program on subjective experience of fatigue (point estimate= -1.65, 95% CI -4.15 to -0.36). The mediation effect averaged about 26% of the total treatment effect.

Regarding self-regulation skills, there was a significant difference (t=2.89 *p*=.006, 95% CI 0.15 to 0.83, *g*=0.72) between the intervention (M=3.68, DP=0.51) and the control group (M=3.19, DP=0.82) at T2. Mediation analyses showed a significant indirect effect of treatment through the use of self-regulation skills (T2) on fatigue at T3 (point estimate= -2.22, 95% CI of -5.41 to -0.56), accounting for 32% of the total effect.

Discussion

This trial tested the medium-term (12-months follow-up) effects of a brief self-regulation (SR) based intervention for patients with unexplained chronic fatigue (4-STEPS), which combined face-to-face motivational interviewing with SR skills training. Post-treatment (3-months) results showed beneficial effects of the 4-STEPS on subjective experience of fatigue (primary outcome) and total fatigue severity [33]. At 12-months follow-up, these beneficial effects were maintained and a larger difference was found for subjective experience of fatigue between groups (6.57). Furthermore, we found an increase from baseline for the number of patients in the intervention group presenting non-clinical levels of fatigue (~21%) in comparison to the control group (0%). In addition, the effects of the intervention on fatigue impact in daily life became significant.

Sustained beneficial treatment effects were also found for health-related quality of life (HrQoL). In fact, larger effects on

psychological HrQoL were found at follow-up in comparison to the 3 months post-treatment results (g=0.33 vs. g=0.57). Treatment effects on additional somatic complaints as well as on psychological distress (depression and anxiety) remained non-significant. These results are in line with the average effects found in previous systematic reviews and meta-analyses of graded exercise and psychological interventions in CF(S) [12, 13]. However, few trials present medium to long-term follow-up effects and there is also heterogeneity in the effects. Two earlier trials with similar treatment duration (3-months) that also provided 2 initial face-to-face sessions and additional self-management manuals focusing on educational and behavioural strategies, differ from each other with respect to follow-up results. While in the trial conducted by Powell et al [19] the authors found large effects of the intervention on fatigue, physical functioning and depression, in the trial by Friedberg and colleagues [54] beneficial effects were only found for fatigue severity.

The results for physical activity (PA) reveal that the intervention has a non-significant effect on number of daily steps. In fact, the average difference in daily steps between the two conditions at 12 months was only ~383 steps/days. The average number of daily steps of participants in each condition met however the recommended guidelines for patients with chronic diseases of minimum 6500-8000 steps/day [55]. Furthermore, the magnitude of the interaction effect between treatment condition and time (baseline to follow-up) on leisure-time PA was small. There was a decrease in PA levels from post-treatment to follow-up in the intervention condition; there was, however, still an increase from baseline to follow-up of approximately 30 minutes/week of leisure-time PA. At the same time, the percentage of physically active participants was maintained from post-treatment to follow-up. It may be that patients, who were physically active at post-treatment, set new personal PA goals that did not focus on increasing PA levels but rather on maintaining PA levels or balance between activities (e.g. accumulation of leisure-time PA with daily steps taken). Many behavioral and psychological trials presenting a graded exercise component have found trivial to small beneficial effects on physical activity and capacity in CF(S) patients [50, 56]. However, very few

studies present follow-up results. These studies also measured physical activity mainly in laboratory settings making use of functional capacity measures [e.g. 57], an accelerometer [e.g. 50] or walking tests [e.g. 58].

Since physical activity is a key target in many interventions designed for CF patients, it is important to analyse if changes in PA actually lead to improved fatigue. In the present study, we conducted a mediation analysis to test if the effect of treatment on subjective fatigue severity at follow-up could be explained by (a) an increase in the number of daily steps (a more objective measure of PA) and (b) progress towards a personal PA goal. Results showed that an increased number of daily steps did not mediate treatment effects on fatigue. A recent study by Wiborg and colleagues [59] analysing the mediation effect of PA on fatigue severity and including data from two CBT trials targeting PA in CFS adult patients [18, 50], did not find a significant mediation effect. However, none of the trials included in the analysis had a significant impact on PA levels. In the present trial the effect of the intervention on daily number of steps at post-treatment was only marginally significant. At the same time, we did find that personal goal progress partially explained the effects of treatment on sustained fatigue improvement. This result suggests that it may not be the mere increase in PA that explain fatigue improvement, but rather the formulation of self-chosen and personally meaningful goals that not only increase the likelihood of goal progress and achievement but can also impact positively on disease related outcomes. Likewise, it may be that flexible PA related goals that take into consideration patients' own symptoms and capability as well as the need to regulate daily activity can also explain the beneficial effects of treatment upon sustained fatigue improvement [7]. Thus, PA goals can facilitate the increase of PA levels and maintain these levels or lead to a more balanced form o PA, taking into consideration other daily activities. Future studies could further explore this by using daily activities diaries or other remote activity monitoring systems.

One of the main targets of the 4-STEPS intervention was to increase patients' use of SR skills [23]. Although recent trials have shown that interventions using a combination of theoretically

derived SR-skills [23, 24] were more effective than other interventions [27, 28], only few studies analyzed the mediation effect of SR-skills on health behavior changes and disease related outcomes [20, 21]. Mediation analysis showed that the effect of treatment on fatigue at follow-up could be partly explained by a treatment effect on SR-skills at post-treatment. Encouraging patients to set personal active goals and providing them with skills to attain these goals seems to explain part of the intervention effect on fatigue severity.

Study limitations

The present study has a number of limitations. First, the small sample size limits the generalizability of our findings. Employing complex moderated mediation models with larger samples can provide more insight in differential effects of SR skills (e.g. self-monitoring) and other proximal targets and explore for which subgroups and in which phases of health behaviour change these interventions works best. Furthermore, the intervention combined motivational interviewing, the use of self-regulation techniques and motivational tools (e.g. pedometer), but the effect of each components could not be separated out in present study. Future studies should address this issue by using a full-factorial design.

Second, this trial was carried out in health care centres and in a patient association. To deal with potential bias the randomisation procedure was stratified by sample, and statistical analyses were conducted controlling for setting. Differences in recruitment strategy within these settings may, however, have led to a selection bias. Third, confirmation of CF(S) inclusion and exclusion criteria was based on self-reported CDC criteria and it can therefore not be excluded that some patients did not fulfill the criteria. Ideally, the diagnosis should also rule out other somatic and psychiatric causes of the symptoms, by means of a full clinical assessment and standardised psychiatric interview. Fourth, men were largely underrepresented in the sample; more studies are therefore needed to determine the effects of this program in men suffering from CF(S). Fifth, due to the fact that there are no normative data for the Portuguese CIS20, comparisons made regarding (non-) clinical levels of fatigue severity should be interpreted with care.

Furthermore, future trials should investigate the benefits of self-regulation based interventions in a design that includes an active control condition, e.g. a treatment such as GET. Finally, we expected a brief intervention with less direct contact to have a lower dropout rate than more lengthy interventions, but this was not the case. Attrition from baseline to 12-months follow-up was however lower in this study than what was recently found in other randomized controlled trials of brief interventions [54, 60].

Conclusion

Despite its limitations, this study found that a brief intervention has sustained small to medium effects on fatigue severity and impact, health-related quality of life, and leisure-time PA. Minimal direct contact interventions that can be easily implemented in standard health care can be useful for patients presenting difficulties in attending regular health care facilities [60] and/or for patients who do not need more intensive forms of treatments [61]. Furthermore, our results suggest that using motivational and self-regulation principles and techniques can lead to improved fatigue in CF(S) patients. Self-chosen, personally meaningful goals appear to motivate these patients, while SR-skills training facilitate the attainment of their goals. By providing continued remote contact with patients, making use of e.g. e-health and m-health in order to provide maintained tailored feedback, intervention effects could be sustained over a longer period of time.

Other information

The trial is registered at http://www.controlled-trials.com, number ISRCTN70763996 and we have previously published the protocol of our trial [32]. This report followed the revised CONSORT guidelines for reporting randomized trials [62].

Acknowledgement

This study was partially funded by the Portuguese Foundation for Science and Technology with a grant to the first author (SFRH/BD/47579/2008). The authors would like to thank all patients that participated in this research, the directors and medical doctors from the Health Care Centres (USF Conde de Oeiras, USF São Julião, USF Marginal, USF Navegantes, Medicil), the volunteers from MYOS, Maria José Vazão, Andreia Cordeiro and Maria João Gouveia.

Author(s) Statement of Conflict of Interest and Adherence to Ethical Standards: Marta Marques, Véronique de Gucht, Isabel Leal and Stan Maes, declare that they have no conflict of interest. Marta Marques has received a research grant from the Portuguese Foundation for Science and Technology (SFRH/BD/47579/2008). All procedures, including the informed consent process, were done in accordance with the ethical standards of the responsible committee on human experimentation (Portuguese Medical-Ethics Committe of the Regional Health Administration guidelines) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients before being included in the study.

References

1. Afari N, Buchwald D. Chronic Fatigue Syndrome: A Review. Am J Psychiatry. 2003; 160: 221-236. doi: 10.1176/appi.ajp.160.2.221.
2. Hardt J, Buchwald D, Wilks D, Sharpe M, Nix WA, Egle UT. Health-related quality of life in patients with chronic fatigue syndrome: an international study. J Psychosom Res. 2001; 51(2): 431-434. doi: 10.1016/S0022-3999(01)00220-3
3. Fukuda K, Strauss S, Hickie I, Sharpe M, Dobbins J, Komaroff A: The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med. 1994; 121: 953 - 959.
4. Fulcher K, White P. Strength and physiological response to exercise in patients with chronic fatigue syndrome. J Neurol Neurosurg Psychiatry. 2000; 69: 302-307. doi:10.1136/jnnp.69.3.302
5. Clark L, Clark P, White. The role of deconditioning and therapeutic exercise in chronic fatigue syndrome (CFS). Journal of Mental Health. 2005; 14(3): 237-252. doi:10.1080/09638230500136308
6. Nijs J, Wallman K, Paul L. Chronic Fatigue Syndrome. In: Saxton J, eds. Exercise and Chronic Disease: An Evidence-Based Approach. New York, USA: Routledge; 2011.
7. Nijs J, Paul L, Wallman K. Chronic fatigue syndrome: an approach combining self-management with graded exercise to avoid exacerbations. J Rehabil Med. 2008; 40: 241-247. doi: 10.2340/16501977-0185.
8. Black C, O'Connor P, McCully K. Increased daily physical activity and fatigue symptoms in chronic fatigue syndrome. Dynamic Medicine. 2005, 4(1): 3. doi:10.1186/1476-5918-4-3
9. Harvey S, Wessely S. Chronic fatigue syndrome: identifying zebras amongst the horses. BMC Medicine. 2009; 7(1): 58. doi:10.1186/1741-7015-7-58
10. Spence M, Moss-Morris R, Chalder T. The behaviour responses to illness questionnaire (BRIQ): A new predictive measure of medically unexplained symptoms following acute infection. Psychol Med. 2005; 35: 583-593. doi:10.1017/S0033291704003484
11. National Institute for Health and Clinical Excellence. NICE clinical guideline 53. Chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy: diagnosis and management of CFS/ME in adults and children. 2007.
12. Castell BD, Kazantsis N & Moss-Morris. Cognitive Behavioral Therapy

and Graded Exercise for Chronic Fatigue Syndrome: A meta-analysis. Clin Psychol Sci and Pract. 2011; 18(4): 311-324. doi: 10.1111/j.1468-2850.2011.01262.x
13. Malouff JM, Thorsteinsson EB, Rooke SE, Bhullar N, Schutte NS. Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: A meta-analysis. Clin Psychol Rev. 2008; 28(5): 736-745. doi: 10.1016/j.cpr.2007.10.004
14. Edmonds L, McGuire L, Price J. Exercise Therapy for Chronic Fatigue Syndrome. Cochrane Database Syst Rev. 2004; 3: CD003200.
15. Price J, Mitchell E, Tidy E, Hunot V. Cognitive behaviour therapy for chronic fatigue syndrome in adults. Cochrane Database Syst Rev. 2008; 3: CD001027.
16. Ridsdale L, Hurley M, King M, McCrone P, Donaldson N. The effect of counselling, graded exercise and usual care for people with chronic fatigue in primary care: a randomized trial. Psychol Med. 2012; 42(10): 2217-2224. doi:10.1017/S0033291712000256.
17. Wearden A.J., Dowrick C., Chew-Graham C., Bentall R.P.,..., Dunn G. (2010). Nurse led, home based self help treatment for patients in primary care with chronic fatigue syndrome: randomised controlled trial. *BMJ, 340*. doi: 10.1136/bmj.c1777
18. Prins JB, Bleijenberg G, Bazelmans E, et al. Cognitive behaviour therapy for chronic fatigue syndrome: A multicentre randomised controlled trial. The Lancet. 2001; 357(9259): 841-847. doi:10.1016/S0140-6736(00)04198-2
19. Powell P, Bentall RP, Nye FJ, Edwards RHT. Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. BMJ. 2001; 322: 387. doi: 10.1136/bmj.322.7283.387
20. Sniehotta FF, Scholz U, Schwarzer R: Bridging the intention–behaviour gap: Planning, self-efficacy, and action control in the adoption and maintenance of physical exercise. Psychol & Health. 2005; 20(2): 143-160. doi:10.1080/08870440512331317670
21. Janssen V, Gucht V, Exel H, Maes S. A self-regulation lifestyle program for post-cardiac rehabilitation patients has long-term effects on exercise adherence. J Behav Med. 2014; 37(2): 308-21. doi: 10.1007/s10865-012-9489-y.
22. Knittle K, Gucht V, Hurkmans E, et al. Targeting motivation and self-regulation to increase physical activity among patients with rheumatoid arthritis: A randomised controlled trial. Clin Rheum. 2013:1-

8. doi:10.1007/s10067-013-2425-x
23. Maes S, Karoly P: Self-regulation assessment and intervention in physical health and illness: a Review. Appl Psychol: Int Rev. 2005; 54(29): 267- 299. doi:10.1111/j.1464-0597.2005.00210.x
24. Carver CS, Scheier MF. On the self-regulation of behavior. New York: University Press; 1998.
25. Sheldon KM, Elliot AJ: Goal striving, need satisfaction, and longitudinal well-being: the self-concordance model. J Pers Soc Psychol. 1999:76(3): 482-497.
26. Miller B, Rollnick S. Motivational interviewing: Helping people change, 3rd edn. NY: The Guiford Press; 2012.
27. Michie S, Abraham C, Whittington C, McAteer J, Gupta S. Effective techniques in healthy eating and physical activity interventions: A meta-regression. Health Psych. 2009; 28(6): 690-701. doi: 10.1037/a0016136.
28. Janssen V, Gucht VD, Dusseldorp E, Maes S. Lifestyle modification programmes for patients with coronary heart disease: A systematic review and meta-analysis of randomized controlled trials. Eur J Prev Card; 2013: 20(4): 620-640. doi: 10.1177/2047487312462824.
29. Nijs J, Paul L, Wallman K. Chronic fatigue syndrome: an approach combining self-management with graded exercise to avoid exacerbations. J Rehabil Med. 2008; 40:241 - 247. doi: 10.2340/16501977-0185
30. Nijs J, Van Oosterwijck J, Meeus M. Myalgic encephalomyeltitis/ chronic fatigue syndrome: Rehabilitation through activity management, stress management and exercise therapy. International Encyclopedia of Rehabilitation; 2013.
31. Wallman KE, Morton AR, Goodman C, Grove R, Guilfoyle AM. Randomised controlled trial of graded exercise in chronic fatigue syndrome. Med J Australia. 2004; 180(9): 444-448.
32. Marques M, De Gucht V, Stan M, Leal I. Protocol for the "Four steps to control your fatigue (4-STEPS)" randomised controlled trial: A self-regulation based physical activity intervention for patients with unexplained Chronic Fatigue. BMC Public Health. 2012; 12:202. doi:10.1186/1471-2458-12-202
33. Marques M, De Gucht V, Maes S, Leal, I. Short term results of a self-regulation based physical activity intervention for patients with unexplained chronic fatigue. Psychol& Health. 2012; 27(Sup1): 84-85.
34. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 8 ed. Baltimore: Lippincott Williams & Williams;

2009.
35. Wagner D, Nisenbaum R, Heim C, Jones JF, Unger ER, Reeves WC. Psychometric properties of the CDC symptom inventory for assessment of chronic fatigue syndrome. Pop Health Met. 2005; 3:8. doi:10.1186/1478-7954-3-8
36. Marques M, de Gucht V, Gouveia MJ, Cordeiro A, Maes S. Psychometric properties of the Portuguese version of the Checklist of Individual Strength (CIS20-P). Psychol, Com & Health. 2013; 22(1): 11-18. doi:10.5964/pch.v2i1.57
37. Vercoulen J, Alberets M, Bleijenberg G. De Checklist Individual Strenght (CIS). Gedragstherapie. 1999; 32: 31- 36.
38. De Vree B, van der Werf S, Prins J, Bazlmans E, Vercoulen J, Servaes P. Meetinstrumenten bij chronische vermoeidheid. Gedragstherapie. 2002; 35:157-64.
39. Cleeland C, Ryan K. Pain assessment: global use of the brief pain inventory. Ann Acad Med Singapore. 1994; 23: 129-138.
40. Wendel-Vos G, Schuit A, Saris W, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56: 1163-9. doi: 10.1016/S0895-4356(03)00220-8.
41. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc. 2000; 32:S498-504.
42. Ainsworth B, Haskell W, Herrmann S,et al. Compendium of Physical Activities: A second update of codes and MET values. Med Sci Sports Exerc. 2011; 43(8): 1575-1581. doi: 10.1249/MSS.0b013e31821ece12.
43. Welk GJ, Differding JA, Thompson RW, Blair SN, Dziura J, Hart P. The utility of the Digi-walker step counter to assess daily physical activity patterns. Med Sci Sports Exerc. 2000; 32(9 Suppl): S481-488.
44. Le Masurier GC, Tudor-Locke C. Comparison of pedometer and accelerometer accuracy under controlled conditions. Med Sci Sports Exerc. 2003; 35(5): 867-871. doi: 10.1249/01.MSS.0000064996.63632.10
45. Maes S, Karoly P, De Gucht V, Ruehlman L, Heiser W. Leiden(NL)/ Phoenix (AZ): Leiden University & Arizona State University; 2006.
46. Ware J, Kosinski M, Turner-Bowker D, Gandek B: Lincoln, RI: Quality Metric Incorporated; 2002.
47. Kroenke K, Spitzer R, Williamsm J. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom

Med. 2002; 64: 258-266.
48. Degoratis L. Brief Symptom Inventory: Administration, Scoring and Procedures Manual. 4 ed: Minneapolis: National Computer System; 1993.
49. Faul F, Erdfelder E, Lang A, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioural and biomedical sciences. Behav Res Methods. 2007; 39:175-191. doi: 10.3758/BF03193146.
50. Knoop H, Van der Meer J, Bleijenberg G. Guided self-instructions for people with chronic fatigue syndrome: a randomised controlled trial. Br J Psychiatry. 2008; 190:340 - 341. doi: 10.1192/bjp.bp.108.051292.
51. Stulemeijer M, de Jong L, Fiselier T, Hoogveld S, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ. 2005; 330(7495): 820. doi 10.1136/bmj.38301.587106.63.
52. Hedges LV. Distribution Theory for Glass's Estimator of Effect size and Related Estimators. J Educ Behav Stat. 1981; 6(2): 107-128.
53. Hayes AF. Introduction to Mediation, Moderation, and conditional Process Analysis: A Regression-based approach. NY: Guilford Press; 2013.
54. Friedberg F, Napoli A, Coronel J, et al. Chronic fatigue self-management in primary care: a randomized trial. Psychosom Med. 2013; 75(7):650-657. doi:10.1097/PSY.0b013e31829dbed4.
55. Tudor-Locke C, Craig CL, Aoyagi Y, et al. How many steps/day are enough? For older adults and special populations. Int J Behav Nutr Phys Act. 2011; 8(1): 80. doi:10.1186/1479-5868-8-80.
56. Moss-Morris R, Sharon C, Tobin R, Baldi JC. A randomized controlled graded exercise trail for chronic fatigue syndrome: outcomes and mechanisms of change. J Health Psychol. 2005; 10(2): 245-259. doi:10.1177/1359105305049774.
57. Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. BMJ. 1997; 314(7095): 1647-1652. doi: 10.1136/bmj.314.7095.1647
58. White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. The Lancet. 2011; 377(9768): 823-836. doi:10.1016/S0140-6736(11)60096-2.
59. Wiborg JF, Knoop H, Stulemeijer M, Prins JB, Bleijenberg G. How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. Psychol Med. 2010; 40(8):

1281-1287. doi:10.1017/S0033291709992212.
60. Burgess M, Andiappan M, Chalder T. Cognitive Behaviour Therapy for Chronic Fatigue Syndrome in Adults: Face to Face versus Telephone Treatment: A Randomized Controlled Trial. Behav Cogn Psychother. 2012; 40(2): 175-191. doi: 10.1017/S1352465811000543
61. Tummers M, Knoop H, van Dam A, Bleijenberg G. Implementing a minimal intervention for chronic fatigue syndrome in a mental health centre: a randomized controlled trial. Psychological Medicine. 2012; 42(10): 2205-2215. doi: 10.1017/S0033291712000232
62. Schulz K, Altman D, Moher D, and the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010; 8(1):18. doi: 10.1136/bmj.c332

Figure 1 Flow diagram of participants through the intervention.

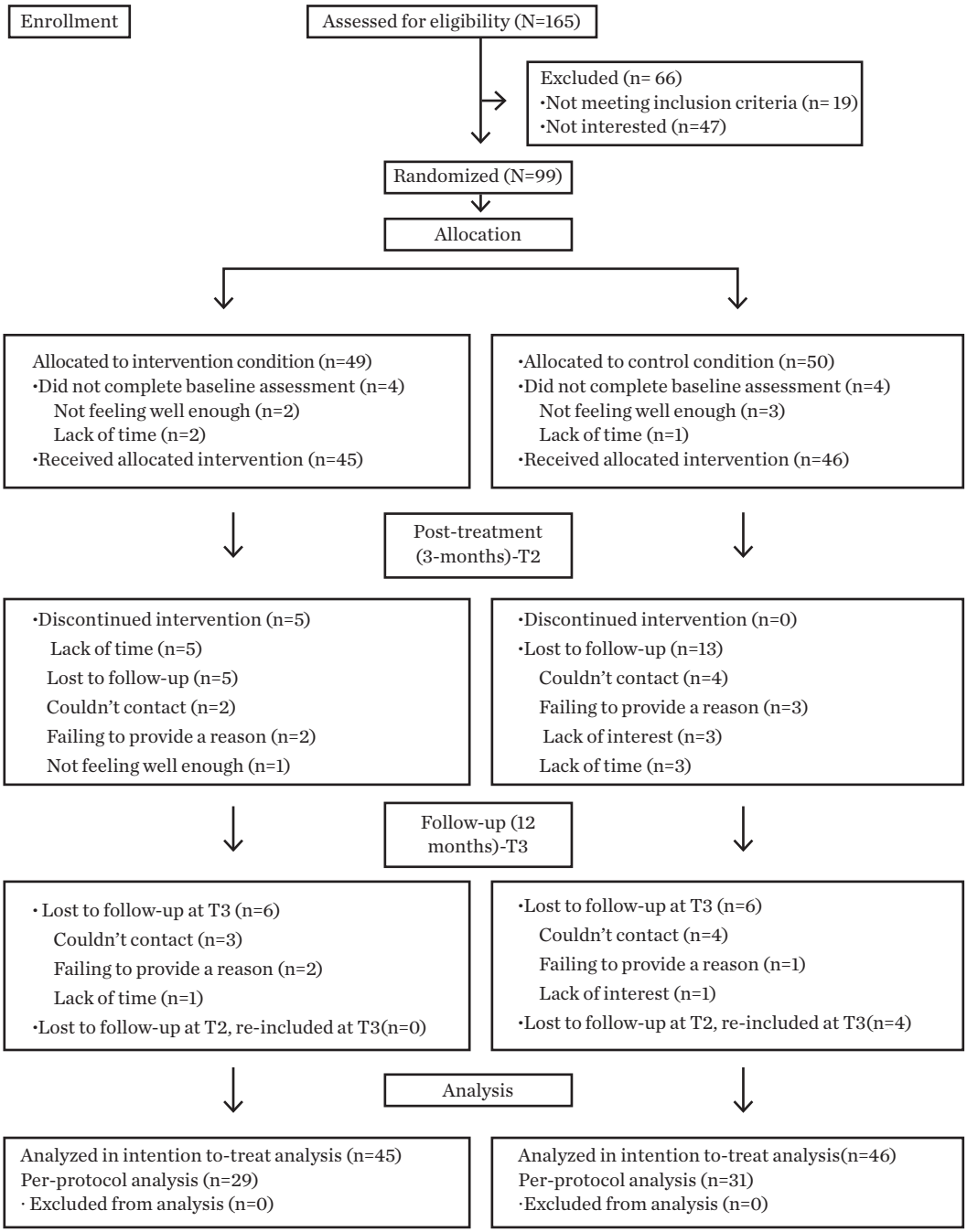


Table 1 Baseline demographics and patient characteristics

Characteristic	**Intervention** (n=45)	**Control** (n=46)	***p***
Age	46.96±10.39	49.20±11.49	0.33
Gender (women)	44 (97.8)	45 (97.8)	1.00
Education			
Primary	12 (26.7)	16 (34.8)	0.65
Secondary	17 (37.8)	17 (37.0)	
Higher	16 (35.6)	13 (28.3)	
Employed	24 (54.3)	25 (54.3)	1.00
Not working due to fatigue [1]	10 (45.5)	11 (47.8)	1.00
Abseentism (n. days) [2]	6.20 ± 10.44	14.36 ± 22.61	0.14
Physically active[3]	15 (33.3)	17 (37)	0.82
Disease duration (years)	9.81 ± 8.02	10.96 ± 9.06	0.53
Number of medical consultations	4.03± 2.88	5.10 ± 4.43	0.20
Number of major CDC CFS symptoms	6.42 ± 1.29	6.70 ± 1.38	0.33
Diagnostic criteria			
ICF	5 (11.1)	3 (6.5)	0.49
CFS	40 (88.9)	43 (93.5)	
Clinical Levels of Fatigue[4,5]			
Yes	42 (93.3)	43 (93.5)	1.00
No	3 (6.7)	3 (6.5)	
Setting			
Health Care Centres	24 (53.3)	25 (54.3)	1.00
Patient Association	21 (46.7)	21 (45.7)	

Note. Values are presented as Mean ± Standard Deviation or Frequencies (%). 1 n=21 in each condition. 2 n=20 (Intervention condition); n=22 (Control condition). 3Results for completers [Physically active: Intervention group = 11/29 (37.9%); Control condition= 13/31 (41%); p= 0.75]. 4Cut-off score of 35 on the Subjective Fatigue sub-scale of the CIS20. 5Results for completers [clinical levels: Intervention group= 28/29(96.6%) and 29/31 (93.5%); p=01.00]. CDC = Centres for Disease Control and Prevention; ICF = Idiopathic Chronic Fatigue; CFS = Chronic Fatigue Syndrome.

Table 2 Changes in outcomes between baseline (T1), post-treatment (T2) and follow-up (T3)

Outcome	**Time**	**Intervention** (n=45)	**Control** (n=46)	**Group x Time interaction[a]**			
				F	*p*	Contrasts	
						Time	*p*
Subjective experience of fatigue	T1	46.00±6.30	47.00±7.66	6.70	.003		
	T2	42.62±9.93	47.35±8.31			T1-T3	.004
	T3	41.96±10.08	48.53±7.92			T2-T3	.140
Fatigue severity[1]	T1	98.40±16.43	103.54±19.07	6.14	.003		
	T2	93.73±22.37	106.76 ±20.32			T1-T3	.003
	T3	92.42±22.30	108.39±20.07			T2-T3	.282
Fatigue impact	T1	6.25±1.89	6.88±1.90	4.12	.018		
	T2	5.89±2.38	6.33±2.21			T1-T3	.436
	T3	5.13±2.52	6.49±2.23			T2-T3	.003
Leisure-time PA[2]	T1	41.56±70.59	58.37 ±106.28	4.83	.011		
	T2	120.67±146.19	57.39± 152.00			T1-T3	.012
	T3	71.67±110.36	66.08±121.17			T2-T3	.054
PA (steps/ day)	T1	6629±2716	6773±2820	1.96	.151		
	T2	7077±2746	6385±2830				
	T3	6941±2728	6557±2949				
Physical HRQoL	T1	38.22±17.78	31.30±18.90	7.06	.002		
	T2	43.33±21.87	28.15±20.23			T1-T3	.002
	T3	42.78±21.20	28.27±19.68			T2-T3	.790
Mental HRQoL	T1	41.57± 16.13	37.59 ±17.62	6.39	.002		
	T2	46.85±19.71	36.79±19.15			T1-T3	.004
	T3	50.39±18.80	36.27±18.35			T2-T3	.063
Somatic distress	T1	14.02±4.04	16.20 ±4.47	0.43	.624		
	T2	13.05±4.72	15.76±4.48				
	T3	13.40±5.50	15.59±4.61				
Depression	T1	1.49±0.88	1.89±0.91	0.48	.605		
	T2	1.55±0.95	1.91±0.93				
	T3	1.39±0.97	1.88±0.98				
Anxiety	T1	1.63±0.77	1.66±0.79	1.01	.365		
	T2	1.44±0.79	1.64±0.81				
	T3	1.37±0.81	1.61±0.86				

(Note. Values are presented as mean ± standard deviation. [a]Mixed design repeated measures using intention to treat analysis, adjusted for disease duration and setting (Health care centres vs. Patient association).[1]CIS20 total score. [2]Descriptives are presented in raw form. PA= physical activity. HRQoL= Health-related quality of life.

Table 3 Summary of mediation analyses predicting levels of fatigue severity at follow-up

	Mediators		
	Daily steps	Goal progress	Self-regulation skills[a]
Paths a (IV →M)	666.47	1.65*	0.49**
Paths b (M→DV)	-0.00	-4.65*	-4.55*
Path c (total effect IV→DV)	-6.31**	-6.31**	-7.02**
Paths c' (direct effect IV→DV after controlling for M-	-5.83**	-4.63**	-4.80*
Estimate of indirect effect (axb paths)	-0.47	-1.65	-2.22
95% CI of indirect effect	-1.92 to 1.49	-4.15 to -0.36	-5.41 to -0.56
Effect ratio of indirect effect	0.07	0.26	0.32

*Note . * p < 0.05, ** p<0.01 CI=Confidence Interval; IV Independent Variable (treatment condition); DV Dependent Variable (subjective fatigue severity); M Mediator . [a] Sample size corresponds to completers dataset, as SR skills was only assessed at T2 (n=35 in intervention group and n=33 in control group).*

08

Summary & General Discussion

The focus of this thesis was on the role of self-regulation and physical activity in chronic fatigue management. Idiopathic Chronic Fatigue (ICF) and Chronic Fatigue Syndrome (CFS) are of unknown aetiology, but research suggests a multifactorial nature in which biological/physical, psychological and social factors interact [1, 2].

Treatment approaches target mainly perpetuating factors of fatigue chronicity, such as lack of physical activity (PA). Adopting a health behaviour change framework can thus contribute to the understanding and promotion of PA in CF(S) patients. One of the theoretical perspectives on health behaviour change is Self-regulation (SR), which postulates that behaviour is a goal driven process, in which motivational and volitional aspects interact [3]. SR based interventions have demonstrated to be effective in promoting long-lasting health behaviour change in chronic disease populations [4-7].

The main purpose of this thesis was to develop, implement and evaluate the effects of a SR-based intervention targeting PA, the "4-STEPS to control your fatigue" trial on chronic fatigue management among patients with CF(S). We also intended to examine whether changes in the intermediate targets of the intervention (self-regulation skills and physical activity) explained subsequent changes in fatigue severity.

Prior to this intervention study we conducted a series of studies that were important for the development and evaluation of the 4-STEPS Randomized Controlled Trial (RCT): (1) a validation of a measure of fatigue severity (primary endpoint) for the language and population in which we intended to implement the intervention (Portugal),(2) a comparison of clinical characteristics and behavioural and cognitive determinants of CFS in a Dutch and a Portuguese patient sample, and (3) a systematic review and meta-analysis of behavioural and psychological interventions with a graded PA component conducted with CF(S) patients.

In this chapter, we first present a summary of each empirical study. Next, we present a theoretical integration of findings and

implications for practice, followed by a number of methodological considerations with a focus on the strengths and limitations of the 4-STEPS trial. Finally, possible avenues for future research and concluding remarks are addressed.

Summary of Studies

Assessment of Fatigue

The first empirical study (**Chapter 2**) described the psychometric properties of the Portuguese Version of the Checklist of Individual Strength (CIS20-P; [8]). The main reason for conducting this empirical study is that fatigue severity is the primary endpoint of the 4-STEPS trial. Therefore, we intended to use a measure with adequate psychometric properties for the language and population of interest, allowing at the same time the assessment of fatigue according to international standards. The CIS20 [9, 10], a multidimensional self-report instrument incorporating both physical and mental fatigue, is a well validated measure developed for CFS patients that has been widely used within this (e.g. [11, 12]) and other populations (e.g. working population; [13]), especially in the Netherlands. For the purpose of this study, data was collected from a large sample of healthy adults (N= 430) and a sample of CF(S) patients (N=89).

Our findings were similar to what was found in previous research [14], although studies examining the factorial structure of the CIS20 are scarce. Convergent validity of the CIS20-P with the Vitality Scale and Physical and Psychological Functioning (assessed by the SF-12v2 [15]) was good. The CIS20-P was also able to adequately discriminate between matched healthy and CF(S) samples. Patients with CF(S) presented significantly higher levels of fatigue on all subscales and on total fatigue severity (Total CIS20-P). Internal consistency estimates of each subscale and total CIS20-P were satisfactory, with the exception of Motivation. Furthermore, results supported a multidimensional (four-factor) structure of the CIS20-P, but some of the adjustment indices of fit to the model were unsatisfactory, especially in the CF(S)

sample. The small sample size of the CF(S) group may explain why estimates were in general poorer within this group.

In the subsequent studies presented in this thesis, only the Subjective Experience of Fatigue subscale measuring general fatigue severity (e.g. "I feel weak") and the total CIS20-P were considered. The choice for selecting the subscale Subjective Fatigue as the primary outcome in the 4-STEPS trial was based on the fact that most trials using the CIS20 typically use this subscale as their primary endpoint.

From Determinants...

Chapter 3 focused on the cross-cultural comparison of clinical characteristics as well as on the behavioural and psychological determinants of CFS between a Portuguese and a Dutch CFS patient sample. Due to the fact that there was no published research conducted in CFS patients in Portugal, and that most trials targeting these patients are conducted in Northern European countries this comparison was important in view of culturally adapting existing CFS models and developing tailored treatment strategies.

We conducted a comparative survey based study with matched samples (female patients with CFS) from the Netherlands (N=167) and Portugal (N=85). The objective of this study was threefold. First, it compared fatigue impairment and severity, somatic distress, psychological distress (depression and anxiety) and physical and psychological Health-Related Quality of Life (HrQoL) in Portuguese and Dutch CFS samples. Second, it examined the contribution of fatigue severity and somatic complaints to HrQoL in Portuguese and Dutch CFS patients. Third, it explored differential effects of self-regulation cognitions (illness beliefs) and behaviours (physical activity and erratic behaviour regulation patterns – limiting behaviour and all-or-nothing) on fatigue severity.

As expected, there were similar levels of fatigue severity in both samples, which supports the validity of the CIS20 to assess fatigue across different CFS samples. The levels of somatic distress, the poor physical and mental HrQoL and the high rate of patients not working in both samples, reflect the disability commonly found

in CFS patients [1]. Furthermore, we found that higher levels of fatigue and additional somatic symptoms were related to poor HrQoL. In addition, the Portuguese sample demonstrated worst psychological functioning, and higher levels of depression and anxiety. In fact, more than half of the Portuguese CFS patients met clinical levels of psychological distress.

Regarding the third objective of this study, we found that both self-regulation cognitions (illness beliefs) and behavioural factors (physical activity or certain behaviour regulation patterns) were significantly associated with fatigue severity in both samples. Regarding self-regulation cognitions, which according to Leventhal's illness cognition model [16] trigger subsequent (un-) adjusted coping behaviours, our findings are in line with previous research showing that positive illness beliefs are associated with lower fatigue severity and negative beliefs with higher fatigue severity [17]. However, there were differences in specific beliefs. For the Portuguese sample we found that attributing more symptoms to the illness (seriousness of CFS) and reporting a higher emotional impact of the experience of CFS was associated with worse fatigue severity. In relation to the behavioural determinants in the Portuguese sample, higher levels of physical activity were positively associated with fatigue improvement and, on the contrary, limiting behaviour (i.e. excessive resting and marked decrease in daily activities) [18] was associated with worst fatigue levels. This is in line with previous research and current recommendations for CFS patients [19]. In the Dutch population, in which levels of physical activity were higher, adopting an erratic all-or-nothing behaviour regulation pattern (i.e. systematic alternation between periods of over activity and excessive resting as a consequence) was significantly associated with worse fatigue severity. These findings show similarities and differences in clinical characteristics and cognitive and behavioral determinants of CFS that are important for treatment.

...to Interventions

Next, **Chapter 4** presented a systematic review and meta-analysis on the efficacy of behavioral and psychological treatments for

patients with CF(S) focusing on graded PA. Physical activity is considered a key factor in chronic fatigue management, and is therefore targeted in current recommended non-pharmacological treatments for CFS, such as Graded Exercise Therapy (GET) and Cognitive-behavioral Therapy (CBT). None of the published meta-analysis [20, 21] assessed so far the efficacy of these treatment approaches upon physical activity. The first objective of this meta-analysis was to evaluate the overall effect of interventions on PA as well as on fatigue severity, physical functioning and psychological distress (anxiety and depression), among CF(S) patients. Only RCTs were included, in which intervention conditions were compared with either passive control conditions (e.g. waiting list) or active controls (e.g. flexibility/ relaxation).

Overall, results showed that interventions (k=16) had beneficial medium effects on fatigue improvement, and small effects on physical functioning/impairment, physical activity/capacity and psychological distress (depression and anxiety), at post-treatment and at follow-up (up to 17 months). There was an exception for PA at post-treatment for which only a near-significant effect was found.

As treatment effects varied widely between trials, potential moderators of interventions effect were also examined in the meta-analysis. These included the type of care provided to the control condition, treatment setting, length of the intervention, provider of treatment, presence of a psychological (cognitive) component (vs. only behavioural), minimal direct contact between patient and provider (vs. more intensive interventions), and a flexible approach to physical activity (adjustment in PA levels/ goals according to individual tolerance level). Although the small number of studies somewhat limit the conclusions that can be drawn from these subgroup analyses, results showed that some of the variables were moderators of interventions effect but only for Fatigue Severity and Depression. Interventions provided by psychologists/psychotherapists and interventions conducted at secondary or tertiary settings presented larger benefits. In addition, interventions providing minimal direct contact with patients had additional beneficial effects upon fatigue severity and depression. Furthermore, we found that interventions allowing

flexibility in physical activity levels and goals, presented higher effects on depression. We did not find a significant difference in effects between interventions focusing on physical activity only or also targeting psychological factors (e.g. CBT approach), though results point towards a greater effect of this last treatment modality on both fatigue and depression. These results provide valuable indications for the targets and format of future interventions for chronic fatigue management.

Informed by the previous studies, **Chapter 5** presented the protocol of the "4-STEPS to control you fatigue" trial. In the study protocol we presented the theoretical and empirical rationale for developing and implementing the 4-STEPS with CF(S) patients, the aims of the RCT, and a detailed description of the methods and procedures (study design, recruitment and randomization procedures, intervention content and materials, outcomes assessed and data analysis plan).

The 4-STEPS trial was tested in several Primary care centres and in the Portuguese Patient Association. Eligible patients who were willing to participate in the RCT were randomly allocated to either the control (usual care + leaflet with PA-related information) or the intervention condition (usual care + 4-STEPS). The treatment condition received a brief intervention (12 weeks) with minimal direct contact (up to 3 hours of total contact time). The 4-STEPS consisted of a combination of Motivational Interviewing [22], with SR-skills based training. Participants set and planned a relevant PA goal, and were advised to gradually increase PA according to a personal flexible scheme [23]. Patients received manuals with information about CF(S) and physical (in-)activity and received SR based manuals which incorporated SR cognitions and skills for each phase of the goal-related process (goal selection/setting, active goal pursuit and goal attainment/maintenance). To support patients during this process, patients received additional telephone SR-based counselling, as well as a pedometer and daily activities diaries, which could be used to monitor daily activity patterns during the intervention period. Finally, participants received a leaflet

with information of CF(S) to give to their partners of significant other.

Assessments were conducted at baseline, post-treatment (3-months) and at follow-up (12-months). Primary outcome was subjective experience of fatigue (CIS20-P Subjective Experience of Fatigue subscale). Secondary outcomes analyzed in the articles presented in this thesis were fatigue severity (Total CIS20-P), fatigue impact, Health-related Quality of Life (HrQoL; dimensions of physical and psychological functioning), somatic distress and psychological distress (depression and anxiety). To capture different forms of PA in which CF(S) patients may engage in, we assessed (1) daily steps taken (pedometer), (2) Leisure-time PA (Moderate to vigorous PA), and (3) personal elicited PA goal progress and achievement. In addition, we assessed at post-treatment the use of Self-regulation (SR) skills to achieve personal elicited goals.

Post-treatment results of the 4-STEPS trial were reported in the empirical study presented in **Chapter 6** and follow-up results were reported in **Chapter 7**.

Data from eighty-four patients who were equally randomized to treatment conditions and completed baseline assessment was analyzed. Most patients were middle-age (~48 ys.) women (97.8%), and about half of the sample was unemployed. At baseline, only a third of the participants were physically active, doing an average of ~50 minutes per week of leisure-time PA and ~6700 steps/day. Only two participants discontinued the intervention, and total attrition was 25% to post-treatment and 33% to follow-up.

In general, results are in line with what is reported in previous reviews and meta-analysis of trials conducted with CF(S) patients [20, 21, 24, 25], including the meta-analysis presented in this thesis. At post-treatment, there was a significant difference between the intervention and control group of medium magnitude. Likewise, mixed design analysis, controlling for disease duration and setting, showed a significant time by group effect on fatigue severity improvement (Subjective Experience of Fatigue and Total CIS20). In addition, patients who received the 4-STEPS program showed a significant improvement in physical and psychological

HrQoL. In contrast, we did not find significant effects of the 4-STEPS in reducing psychological distress (depression and anxiety) nor somatic distress (additional somatic complaints). Physical activity was one the main targets of the 4-STEPS trial. At post-treatment, we only found a near-significant effect of the intervention on the average number of daily steps. Regarding leisure-time PA there was a marked increase from baseline to post-treatment in the intervention group, by an average of ~80 minutes per week. In addition, there was a significantly greater number of physically active participants in the intervention group (74%; vs. 33% in the control group). Furthermore, a large effect of the 4-STEPS was found on patients' progress in attaining a personal elicited PA goal.

At follow-up (Chapter 7), a larger difference in subjective experience of fatigue between treatment and control conditions was reached (6.6 points; g= 0.72), and there was a marked increase by approximately 21% in the number of patients presenting non-clinical levels of fatigue in the intervention group compared to none in the control group. From post-treatment to follow-up, beneficial effects of the 4-STEPS upon fatigue severity were maintained with larger effects from baseline, and there was an additional significant effect for fatigue impact in daily life. Similarly, we found sustained beneficial effects for physical functioning and larger effects on psychological HrQoL. Treatment effects on somatic complaints and psychological distress (depression and anxiety) remained non-significant. Regarding physical activity, differences between groups on daily steps became meaningless at follow-up. Nevertheless, average of daily steps in each condition met minimal guidelines for patients with chronic diseases [26]. Regarding leisure-time PA, there was no significant time by group effect from post-treatment to follow-up. Although there was a decrease in physical activity levels in the intervention condition, it was still higher than the levels presented at baseline (+ 30 minutes/week). Similarly to what was observed at post-treatment, there was a significantly greater number of physically active participants in the intervention condition (66%; vs. 36% in the control group).

The last objective of this thesis, presented in **Chapter 7**, was to analyze the mechanisms by which the intervention produced sustained effects on the primary endpoint of the 4-STEPS trial (subjective experience of fatigue). For this purpose, we conducted simple mediation analyses investigating the contribution of the empirically and theoretically derived intermediate targets of the 4-STEPS - physical activity and self-regulation skills -, to fatigue improvement.

Regarding PA, we conducted mediation analysis with daily steps taken assessed by a pedometer (near-objective measure of PA) and perceived PA goal progress. Our results showed that fatigue improvement at follow-up could be partially explained by participants' progress and achievement of personal PA goals at post-treatment. In relation to the use of SR skills in pursuing personal behavior change goals, at post-treatment, participants in the intervention group reported a greater overall use of SR-skills (action planning, self-monitoring, seeking feedback, focus attention of goal, emotion regulation, coping with problems and goal persistence) in comparison to those in the control condition. Mediation analysis revealed that increased use of SR strategies to achieve personal behavior change goals (at post-treatment) contributed to improved fatigue reported at follow-up.

The results from the 4-STEPS trial show that a brief self-regulation based intervention can have a beneficial and sustained impact in chronic fatigue management and that progress and achievement of personal PA goals and increase use of SR-skills are at least partly responsible for this sustained improvement in fatigue.

General Discussion

Theoretical Integration and Translation into Practice

In this thesis we intended to examine if a self-regulation based approach would add to the current psychological and behavioral models and treatments for chronic fatigue management.

Is a Self-regulation Framework Useful for CF(S) Management?

Central in self-regulation theories is the assumption that human actions are goal-oriented and that self-regulation concerns cognitions, emotions, and skills that guide the achievement of personally relevant goals [3, 27]. Thus, behavior change is a dynamic goal-guidance process consisting of a goal selection and setting phase, active goal pursuit and goal attainment phase, in which motivational and volitional aspects interact [3]. By using the Motivational Interviewing method and Self-regulation skills based manuals, the 4-STEPS trial targeted all phases of the goal-guidance process, based on the set of guidelines for interventions formulated by Maes & Karoly [3]. In Chapter 3, we examined how illness beliefs derived from Leventhal's illness cognition model [16], contribute to fatigue severity in two patient samples. In line with previous research [17, 28], we found that negative illness beliefs, such as the belief that one has a severe illness with serious consequences, as well negative emotional responses, were associated with worst fatigue severity. If patients experience many symptoms, which may even be misattributed to the disease, this can lead to a hypersensitivity and hypervigilance to somatic symptoms that will confirm illness identity and perceived consequences [17]. On the other hand, positive illness beliefs such as believing that one is in control of CFS were associated with improved fatigue severity.

For this reason, providing patients with clear information on the symptoms associated with CF(S) and how self-regulation strategies can positively impact chronic fatigue was an important first step in view of intervention [3]. In the 4-STEPS intervention (Chapters 5, 6 and 7), patients were initially provided with information regarding CF(S) symptoms, perpetuating factors, and self-management of CFS, to clarify maladaptive illness perceptions in order to facilitate the formulation of more adaptive and positive goals.

Goal setting is a central component of interventions based on a self-regulation framework [3]. Several theoretical considerations should be made in this respect. First, according to self-regulation theories (e.g. Carver and Scheier's Control Theory [27]) goals are hierarchically organized and interconnected; from lower-order concrete goals (so-called "do" goals, e.g. do physical activity) to higher-order abstract goals (so-called "be" goals, e.g. be loved). This means that the formulation of and commitment to particular health behavior goals will depend on the degree to which lower-order goals facilitate or conflict with the achievement of higher-order goals, as well as with other personal goals, at the same hierarchical level, that are valued by the individual (multiple goal pursuit). Goal conflict and goal facilitation are therefore considered to be of importance in all goal-related phases. In the 4-STEPS trial, through the use of Motivational interviewing, the link between physical activity and core values for patients was explored and established by the patients themselves, i.e. how being physically active could fulfil other important goals such as recovering from CF(S), or even more broader goals such as being cared. By doing this exercise, an increase in the personal relevance of health goals and motivation to change was expected. Likewise, during the MI sessions and in the self-regulation skills manual, patients were prompted to identify and prioritize conflicting goals with PA.

Second, choosing and setting personally salient goals (goal ownership), rather than assigned goals, increases the likelihood of goal achievement as patients will be more committed and engaged in the process of goal striving [3, 27, 29]. Moreover, research derived from Self-Determination theory [29, 30], has shown a relation between autonomous motives for goal pursuit and goal attainment [31], as well as with the adoption and maintenance of physical activity in healthy and chronic disease populations [32]. By evoking patients' motives and strengthening confidence to change in an autonomy-supportive environment, we could prompt the formulation of personally salient and self-chosen goals. In the 4-STEPS trial we found that progress and achievement of personal physical activity goals contributed to sustained improved fatigue (Chapter 7). Third, according to a Self-regulation perspective [27], one of the

triggers of motivation to change and selection of behaviour change goals is the perceived discrepancy between an individual current state (input value) and a desired state (reference value), through a comparator (e.g. self-monitoring). By identifying discrepancy it will prompt individuals to seek a reduction in the discrepancy towards the desired state. CF(S) patients tend however to adopt a discrepancy system that reinforces their *status quo* as their reference value is frequently based on symptom avoidance (e.g. activity avoidance) [33]. One way in which we targeted discrepancy during MI was by eliciting the association between the current behaviour and important life goals/values (aforementioned activity) and by resolving the ambivalence that can contribute to moving from keeping the *status quo* to engage in behavior change, which, in turn, can lead to improved fatigue and well-being. In addition, from the first to the second MI session patients monitored their daily activity levels by means of pedometer and daily activities records, which provided the necessary feedback to trigger discrepancy reduction (i.e. behaviour change goal). By experiencing a gradual increase in physical activity without exacerbation patients are expected to adopt more positive reference values that will encourage them to formulate active and positive goals instead of avoidance behaviours [33].

To enhance the process of formulating health-related goals (e.g. physical activity) and pursuing them, several self-regulation skills are considered to play an important role [3, 34]. First, action planning (i.e. detailed plans of what, how, when, where, and with whom) is consider to promote a transition from intention to action. Research has shown the beneficial effects of action planning and implementation intentions for health behaviour change [35] and goal achievement [36]. In the 4-STEPS trial, only patients in the intervention group were supported to formulate such a detailed plan to achieve a physical activity goal, resulting in a significantly higher level of goal progress and achievement in the treatment group (Chapter 6).

Second, prompting self-monitoring of behaviour and obtaining progress-related feedback is a critical component of successful self-regulation [3, 34], as it serves to focus one's attention on behaviour/goal progress and make the necessary adjustments in accordance.

To facilitate self-monitoring and progress-related feedback, we used several strategies: (1) patients were offered pedometers, which promoted sustained monitoring of physical activity and immediate feedback, (2) we provided daily activities records (to identify and monitor behaviour regulation patterns), (3) participants set incremental goals (goal laddering), which allowed patients to check their progress for each goal step, and (4) we provided subsequently brief telephone counselling, which was also a form of providing feedback by revisiting goals that patients had previously formulated.

Finally, participants were prompted to plan how to cope with anticipated barriers to behaviour change. A recent systematic review [37] shows that interventions combining action and coping plans were more effective than interventions targeting action planning alone, and that supporting participants in the process of forming plans to prevent relapse increases intervention effectiveness. A coping planning or problem solving activity was presented in the self-regulation skills manual and it was the main focus of the telephone counselling sessions.

The results of the 4-STEPS trial (Chapters 6 and 7) demonstrated that the strategies employed lead to a higher use of SR-skills to regulate one's own behaviour in the treatment condition in comparison to the control condition leading to an increase in physical activity in the intervention group. Furthermore, the use of these skills significantly contributed to sustained improved fatigue. These results are in line with previous research showing the beneficial sustained effects of targeting SR-interventions in patients with chronic diseases [4, 5, 38]. Likewise, recent meta-analyses found that interventions combining SR-skills derived from Self-regulation theory (e.g. Control Theory [27]), were more effective than other interventions in the general population [34] and in patients with chronic disease [39, 40]. Unfortunately, the limited information regarding the content of the interventions included in the meta-analysis (Chapter 4), did not allow the coding and examination of potential moderation effects of specific self-regulation principles as a moderator of intervention effects (e.g. goal setting).

Why and How to Target Physical Activity for CF(S)

Management?

Extensive literature has demonstrated that physical inactivity and excessive resting are perpetuating factors of fatigue chronicity in CF(S) patients and that PA based on a graded activity approach can lead to improved health-related outcomes in CF(S) patients [1, 41].

In this thesis our aims regarding PA were to (1) examine physical (in-)activity behaviour in a Portuguese sample of CF(S) patients in order to inform key targets of the 4-STEPS trial, (2) to analyze whether available interventions had a positive effect on PA, (3) whether a self-regulation approach would have a beneficial impact in improving PA among CF(S) patients, and (4) whether PA was in fact related to improved outcomes in CF(S).

In Chapter 3, we found that Portuguese CFS patients were characterized by low levels of PA, and that these levels as well as limiting behaviour were associated with fatigue severity, pointing at the need to address PA in interventions for chronic fatigue management in this population.

In Chapter 4 we analyzed the effects of behavioral and psychological interventions with a graded activity component in increasing PA. Although there were few studies including PA as an outcome, our results showed that the overall effect of interventions on physical activity/capacity was either non-significant or small. None of the moderators analysed explained the heterogeneity found between studies. The fact that physical activity interventions had only limited impact on PA is worth addressing. This could be due to variability in assessment methods of PA used in the trials (walking tests, accelerometers or physiological measures) or to other potential moderators that were not included in this meta-analysis (e.g. type of PA). It also points at the need of testing other forms of interventions that may be more successful in promoting physical activity (e.g. motivational and self-regulation approaches), as we did in the 4-STEPS trial.

The fact that Portuguese patients presented with low levels of physical activity justified the adoption of an intervention combining motivational interviewing, aiming at strengthening patients own motivation and confidence to engage in personal relevant health-behaviour goals, with self-regulation skills training

to support the process of goal setting and pursuit.

Recent literature suggests that graded activity approaches rather than adopting a rigid model of gradual increases in the frequency and intensity of physical activity, independently of symptoms experienced, should promote flexibility in PA levels and goals that patients adopt on a daily basis with a personal balance between daily activities and with rest (pacing) [23]. This approach can prevent overexertion, a major symptom in CFS that contributes a boom-and-bust pattern of activity and thus to the perpetuation of fatigue, [19, 23]. In the meta-analysis presented in Chapter 4 we found that interventions incorporating a flexible approach to PA levels or goals had also beneficial effects on depression ($p<.10$) and a slightly larger effect on fatigue severity. In the 4-STEPS trial, we adopted this approach to PA.

Results of the 4-STEPS trial showed variability between different PA-related outcomes. Effects on increase daily steps were trival, but moderate to large effects were found for leisure-time PA and progress towards a personal PA goal at post-treatment. The fact that the percentage of active patients in the intervention group remained stable from post-treatment to follow-up in spite of a decrease in leisure-time PA, points at the possibility that patients may have set new goals not targeting an increase in PA levels, but focusing on e.g. flexibility in PA levels or on a balance between different forms of PA or daily activities.

Furthermore, we found that progress toward a self-chosen PA goal contributed to the explanation of the effects of the 4-STEPS on fatigue improvement, contrarily to what we found for daily steps taken. Previous research analyzing the mediation effect of PA (assessed by means of accelerometer), using data from three RCTs, did not find significant mediation effects nor significant intervention effects on increasing PA [42]. In addition, a recent study found that perceived activity (assessed with a modified version of the subscale Daily Activities of the CIS20) and not objective activity (also assessed by means of accelerometer) explained the variance in fatigue during a CBT based treatment [43]. Our findings point at the benefits of setting personally meaningful PA goals on physical activity and, as a result, improved fatigue. Possible explanations for this mediation effect, are that

patients by identifying that they are progressing towards their own physical activity goal, may experience a change in other cognitive factors such as focus less on symptoms and negative consequences, get a higher sense of control over fatigue, feel more confident in their ability to continue on making the necessary efforts and changes to recover from fatigue, feel more satisfied with their progress, and/or increase their sense of goal ownership, leading to better disease management and improvement [3, 33, 44-46].

Implications for Practice

Findings from the studies reported in this thesis show that focusing on identifying self-regulation factors that influence CF(S) outcomes, can lead to better care for patients with CF(S). The mediation effects found for self-regulation skills and personal goal progress (Chapter 7) indicate that assessing and targeting SR mechanisms can indeed lead to disease improvement. It is however important that health care professionals have access to guidelines that best inform on how to target these mechanisms. To translate SR theory to practice, Maes and Karoly [3] developed a set of principles to guide interventions targeting illness self-regulation, from which the 4-STEPS trial was derived. By providing these guidelines, self-help materials, and adequate training, we can support health professionals in increasing patients' skills to regulate their own behaviours and implement strategies for CF(S) management. Likewise, health care professionals can be trained on how to prompt health behaviour change by applying Motivational Interviewing principles in routine practice. In fact, there has been an increase in Motivational Interview interventions conducted in primary care [47]. Nonetheless, the results from our meta-analysis (Chapter 4) point at additional benefits of treatments provided by psychologists or psychotherapists and the 4-STEPS trial was also conducted by a health psychologist. This finding and the fact that CF(S) seems to result from a multiplicity of determinants, including cognitive, emotional and behavioural factors, reinforces the importance of a multidisciplinary approach in the treatment of CF(S) including psychologists.

The fact that the 4-STEPS is a brief intervention, consisting of a combination of minimal personal contact with health care

professionals, brief telephone counselling and self-regulation based manuals to support CF(S) patients in changing their physical (in-) activity behavior, can be seen as an advantage as it can be offered as an adjunctive treatment for CF(S) in outpatient care. In fact, interventions with minimal direct contact that also allowed for flexibility in PA, provided continuous remote contact to support patients and provided patients with self-management strategies have larger effects on fatigue severity and depression (Chapter 4). Supporting patients' autonomy over their own process of behavior change and providing them with the resources and skills to self-regulate and achieve personal goals seems to be crucial in this respect.

Notwithstanding its potential, the 4-STEPS needs to be assessed for cost-effectiveness and standardized treatments for CF(S) patients in Portugal are yet to be implemented. Several barriers can be identified to the implementation of evidence-based treatments and standardized procedures for the diagnostic and managements of CF(S) in the Portuguese health care system. The first of which is the fact that CF(S) is not recognized as a discrete disorder by primary health care professionals and when referred to secondary-tertiary care, these patients are followed in different medical specialities based on the main symptoms presented by patients to their medical doctor (e.g. rheumatology, internal medicine, neurology or psychiatry). Second, the lack of psychologists in the Portuguese National Health care system that was recently reported by the Portuguese Association of Psychologists can be a major obstacle to the implementation of self-regulation based interventions in health care [48]. Furthermore, the implementation of psychological and self-regulation based treatments for CF(S) patients will depend on the funds available, and the financial constraints that the health care system currently face can also be an obstacle to its implementation. At the same time, due to these financial and human resources constraints the development of brief interventions with minimal direct contact can also been seen as an advantage.

The examination of self-regulation and behavioral determinants of fatigue improvement can contribute to develop predictive models that have good validity and that can be cross-culturally

applied, guiding the development of more effective interventions. Developing a diagnostic tool that explores various mechanisms of fatigue perpetuation or improvement, could lead to the development of tailored intervention strategies from which patients can benefit the most.

Methodological Considerations

Several methodological considerations were already made in the different chapters of the thesis. The aim of this section is to outline the main methodological issues of the 4-STEPS randomized controlled trial, and to formulate methodological considerations that should be taken into consideration in future research.

Strengths and Limitations of the 4-STEPS Trial

The 4-STEPS trial was based on previous studies and is characterized by (1) a randomised controlled designed, (2) inclusion of a 1-year follow-up assessment point, (3) current recommendations for CF(S) management, (4) consideration for the specificities of the Portuguese CF(S) population and context, (5) a theoretical perspective (self-regulation theory) and (6) intervention briefness with low participant burden. With this RCT we evaluated the efficacy of a complex behavior change intervention, and potential mechanisms of change (i.e. PA and SR-skills).

Notwithstanding its strengths, this trial has several limitations that were addressed in detail in Chapters 6 and 7. A first limitation is the basis for the power calculation that was used, the difference in subjective experience of fatigue between the intervention and control condition, which does not necessarily correspond to a clinically significant improvement in fatigue. At present, we believe that there are more appropriate approaches for power calculation, such as a difference of 0.5 SD in fatigue severity from baseline in the intervention group [49], the overall effect size obtained in previous meta-analysis of CBT and GET trials [21], or the change in the mean scores within the intervention group [50].

Second, patients were recruited from several Primary Care centres and from a Patient Association. Although recruitment of participants was stratified by setting, there were differences

in recruitment procedures in each setting that may have caused selection bias. While statistical analyses used to evaluate the effects of the 4-STEPS trial, controlled for potential confounding effects of the type of setting (Health care centres vs. Patient Association). On the other hand, one of the strengths of this trial is that it was a multi-centre RCT, which allowed the inclusion of a larger number of participants from different locations and targeted a more heterogeneous population, therefore contributing for the external validity and generalizability of the findings. In fact, recent reviews suggest that single-centre trials tend to overestimate effects of trials [51, 52]. Unfortunately, due to the limited sample size recruited in each health care centre, we could not control for the potential differential effects of each centre.

Third, attrition rate to the 4-STEPS trial was higher than what was initially anticipated for a brief intervention, in particular to the follow-up assessment point. The reasons for this attrition rate were not further analysed, although patients were followed and some of the patients that were lost to the post-treatment assessment were re-included at the 12-months period of assessment. Other brief and remote contact interventions have also found high drop-out rates [53, 54]. It should be further explore if e.g. other forms of recruitment and contact with patients, between the end of the intervention and assessment points (e.g. booster sessions) could prevent the high attrition rate found.

Fourth, the fact that the intervention was conducted only by one therapist is a clear limitation of the 4-STEPS trial, as we could not assess the effect of the therapist on the intervention. In addition, due to constraints in available resources we could not assess treatment integrity. In clinical trials using MI it is recommended to assess therapist fidelity to the treatment, as it is the consistent use of MI principles and skills as well as the interpersonal style of the therapist that is thought to influence behaviour change and health-related outcomes [22, 47]. For this purpose, several scales such as the Motivational Interviewing Treatment Integrity [55] have been created. Likewise, we did not assess adherence to the full treatment protocol. Although all participants who completed the 4-STEPS intervention received the two MI sessions and telephone counselling, we do not know how many patients were fully adherent

to the content of the SR-skills manual.

Fifth, as the intervention combined several behavior change methods and techniques, such as the use of pedometers, motivational interviewing and SR-skills training, the effects of the different components of the 4-STEPS trial cannot be disentangled nor could we assess whether this specific combination of techniques was responsible for the intervention effects. Future research should consider using a full factorial design to determine the individual contribution of each component.

Finally, in this controlled trial the 4-STEPS program was compared against a passive control group whose participants only received general information about physical activity and formulated a personal physical activity goal without additional guidelines. Comparing the 4-STEPS with other active treatments (such as GET alone, or educational approaches), is an important target for future research.

Sample and Recruitment Considerations

One of the main limitations of the studies presented in this thesis is the small size of the Portuguese CF(S) sample. There were also large differences between samples sizes in the studies presented in Chapter 2 (Portuguese CF(S) vs. healthy sample) and in Chapter 3 (Portuguese CFS vs. Dutch samples), which limits the conclusions that can be drawn from these comparisons. Furthermore, the sample size lacks power to detect changes in secondary outcomes and mediation effects, limiting not only conclusions that can be drawn from the analysis conducted in the RCT (Chapters 6 and 7) but also the type of statistical models that could be employed.

A second limitation is that only two men with CF(S) participated in the 4-STEPS trial and only women were included in the international comparative study (Chapter 3). Studies have shown that CF(S) is more common among women [56], but report a considerable higher percentage of men suffering from CF(S). Future studies should test for differential behavioral and psychological explanatory models of CF(S) concerning gender and explore the effects of the 4-STEPS in male CF(S) patients.

Another important remark is that the empirical studies presented in this thesis targeted only adult patients with CF(S). More studies

are needed to test differential effects of interventions and the application of a self-regulation perspective on CF(S) between adolescents and adults.

The fact that samples were recruited via Health Care Centres and a Patient Association does not allow to generalize results to the general population nor to attribute differences with the Dutch population only to cross-cultural differences in the international comparative study (Chapter 3). In addition, as aforementioned, differences between settings in the recruitment strategy may have led to selection bias. To overcome this bias, not only recruitment for the RCT was stratified by setting, but also statistical analyses on the effects of the 4-STEPS trial were conducted controlling for the effects of the type of setting (Chapters 6 and 7).

The fact that inclusion/exclusion criteria were not verified by means of full laboratory examination and a structured psychiatric interview, may have led to the inclusion of patients with misdiagnosis and/or co-morbidity with other psychiatric and physical clinical conditions, such as Fibromyalgia, as there is a considerable proportion of patients presenting with both CF(S) and Fibromyalgia [1]. This possible co-morbidity with undiagnosed psychiatric disorders may in part explain the difference in psychological distress and psychological HrQoL found between the two cohorts in the cross-cultural study (Chapter 3) as well as the trivial impact of the 4-STEPS upon psychological distress (Chapters 6 and 7). Furthermore, both patients with Idiopathic Chronic Fatigue or Chronic Fatigue Syndrome were included, which means that our sample is constituted by patients presenting with different levels of disability and number of major CFS symptoms experienced. Future studies should examine the contribution of Self-regulation models and the efficacy of the 4-STEPS intervention for different levels of disease severity.

Assessment Considerations

In the studies presented in this thesis, we made extensive use of self-report measures, which are susceptible to response bias. Nevertheless, many of the questionnaires used in this thesis are well validated and reliable. In the case of physical activity, although we used a more objective measure to assess physical activity

(pedometers), it was still the individual that registered and provided written information on daily steps taken. As an alternative, future studies could use accelerometers, in which scores are stored into the internal memory of the device and afterwards fed into an external computer. In addition, accelerometers also provide information on physical activities performed at different levels of intensity and sedentary periods, which allows the assessment of daily activity patterns and fluctuations. In this respect, although we provided patients with diaries to register daily activities, we did not use them as an additional assessment measure. Future studies could use these daily records to assess behaviour regulation patterns (e.g. all-or-nothing behaviors).

Moreover, for the assessment of fatigue severity we were not able to establish normative data for the CIS20-P, as we did not have a representative sample of the Portuguese population. As such, comparisons made in the empirical studies regarding (non-)clinical levels of fatigue severity were based on cut-off scores established for the Dutch population, and should thus be interpreted with care. Future studies should examine normative scores and thresholds for clinical levels in representative samples of the general Portuguese population and populations with chronic diseases, so that the CIS20-P can be used as a complementary diagnostic tool of prolonged fatigue severity in both research and clinical practice in Portugal. Likewise, because there is no normative data for the Portuguese population of the measure used to assess depression and anxiety (Brief Symptom Inventory; BSI [57, 58]), cut-off points for (non-)clinical levels of psychological distress in the cross-cultural study (Chapter 3) were also based on normative data from the Netherlands.

Finally, some of the measures used lack a full comprehensive quality assessment for the Portuguese population (e.g. the Self-regulation Skills Battery), or validation of modified versions (e.g. the Fatigue impact scale).

Future Directions

The studies presented in this thesis showed promising findings indicating that a self-regulation framework can add to existing models and treatments for chronic fatigue management.

However, some questions remained unanswered while others were raised throughout the conduction of these studies. In this section we present some avenues for future research focusing on this thesis as a whole.

In the comparison study presented in Chapter 3, we found that a psychological model of CFS is common to patients from different countries, which is an important finding for the development of treatment modalities that can be internationally implemented, but we also found differences between the patient samples. While this first exploratory study has its merits, more research is needed to fully understand cross-cultural patterns of behaviour and self-regulatory factors in CFS. For example, the large difference in psychological distress found between Portuguese and the Dutch CFS patients may in part have to do with the fact that, in contrast to the situation in the Netherlands, CFS is not recognized as a discrete disorder by primary health care practitioners in Portugal. Difficulties in the diagnosis and lack of legitimization of the disease may therefore lead to higher levels of psychological distress [59]. We are currently conducting a longitudinal survey study comparing clinical characteristics, behaviours and self-regulation factors of CFS between patient samples from several European Countries (France, Italy, Netherlands, Rumania and the United Kingdom).

Our RCT (Chapters 5, 6 and 7) showed that using motivational interviewing principles and SR skills training targeting physical activity and CF(S) management leads to beneficial improvements in fatigue, but sustained effects were assessed only at one year follow-up after baseline assessment. Future studies should analyze longer-term effects of brief interventions. So far, only one study using a brief intervention targeting physical activity in CF(S), analyzed its effects at a longer period of time (2 years) [60], but there was crossover between the conditions. In the meta-analysis conducted within this thesis (Chapter 4), the average follow-up period of assessment in the trials included was 13 months. Although we found that the main effects of the 4-STEPS were maintained at follow-up, for some secondary outcomes the impact of the

intervention decreased. To increase the sustained use of self-regulation skills and to optimize long-term effects of brief interventions, other forms of remote contact using m-health and e-health are worth exploring. Using remote technology can for e.g. prompt continuous self-monitoring of behavior and provide tailored feedback.

Identifying psychological and behavioural perpetuating factors of CF(S), can contribute to the development of diagnostic tools and tailored interventions. While we identified important SR cognitions and skills as well as behaviours that are related to fatigue severity, these only explain a part of the variation in this outcome. Other potential determinants and mechanisms of change have been described in the literature that should be explored, such as social factors (e.g. social support), focusing on bodily symptoms, (in-) avoidance behaviour, or balance in daily activity patterns [1, 44, 61]. Future research should use more complex mediation models to explore how changes in physical activity impact on fatigue improvement from a psychological point of view. As previously mentioned in this chapter, from a self-regulation perspective, feeling capable to engage and progress in some form of physical activity (without exacerbating symptoms), cognitive changes (e.g. focus less on fatigue) and feelings of satisfaction with achievements, can positively impact disease management and improvement [3, 44, 45].

Likewise, examining predictive models and effects of this brief treatment for CF(S) on other important outcomes related to CF(S) is necessary, such as recovery from fatigue as well severity of disability and impairment associated with CF(S) (e.g. work, social life).

More research is clearly needed to identify moderators of explanatory models and intervention effects, so that we can better understand under which conditions (i.e. intervention design) and for whom SR based approaches are most effective. Previous moderator analyses on the effects of brief interventions for CFS found that patients with substantial depressive symptoms benefit less from these types of interventions [50, 62]. In the 4-STEPS trial we did find a lower effect than initially anticipated for psychological

distress (especially for depression). The fact that Portuguese CF(S) patients presented with high levels of psychological distress may explain this finding. At the same time, in meta-analyses that also included more intensive CBT interventions for CFS, the magnitude of treatments effect upon anxiety and depression were small ([21], Chapter), and in our meta-analysis we even found that brief interventions had a larger effect on depression improvement (Chapter 4). Although we attempted to target emotional regulation in the 4-STEPS intervention, this component was directed only to the regulation of emotions to achieve personal elicited goals. Thus, patients presenting with clinical psychological distress may need additional forms of treatments for depressive or anxiety disorders.

Other moderators are worth addressing in future research, such as severity of fatigue, co-morbidity with other Functional Somatic Syndromes (e.g. Fibromyalgia), level of physical activity (passive vs. more active patients), mastery in the use of self-regulation skills (high vs. low), combination of SR-skills, or how SR strategies are prompted (e.g. self-chosen elicited goals vs. goals assigned by practitioners; autonomy-supportive or controlled environment). Furthermore, other methodologies such as N-of-1 RCT design can be used to analyse intraindividual effects of interventions, which can be particular useful to better understand who benefits from treatment techniques and to tailor interventions to each individual [63].

Finally, although this intervention was partially conducted in primary care, a health psychologist delivered it. Due to the fact that motivational and self-regulation based interventions as well as interventions for CF(S) management in primary care are usually delivered by other health professionals (e.g. a general practitioner) in brief consultations, more research is needed to optimize existing interventions for CF(S) management in a primary care setting [21, 47, 64].

Concluding Remarks

The scope of this thesis was on the behavioral and self-regulatory factors associated with health behavior change and chronic fatigue management. Informed by preliminary investigations, we developed and implemented a self-regulation based intervention targeting physical activity for CF(S) patients, the "4-STEPS to control your Fatigue".

The 4-STEPS program, which was tested in a multicentre randomised controlled trial, lead to significant and sustained improvements in fatigue and in patients' functioning and quality of life. The 4-STEPS also produced significant effects on the use of self-regulation skills and physical activity, especially progress towards a personal physical activity goal, partially explaining the sustained effects of the intervention upon fatigue severity. Nonetheless, the 4-STEPS also presented limited effects for some of the outcomes assessed.

The limitations of each of the six empirical studies that were reviewed in this chapter point at the need to conduct more research on the behavioural and psychological mechanisms involved in CF(S) management. In spite of these limitations, we believe that this thesis positively contributes to the advance of disease management in CF(S) patients.

References

1. Afari, N., Buchwald, D. *Chronic Fatigue Syndrome: A Review.* American Journal of Psychiatry, 2003. 160: 221-236.
2. Prins, J.B., Van der Meer, J.W.M., Bleijenberg, G. *Chronic fatigue syndrome.* Lancet, 2006. 367:. 346-355.
3. Maes, S., Karoly, P. *Self-regulation assessment and intervention in physical health and illness: a Review.* Applied Psychology: International Review, 2005. 54(29): 267-299.
4. Knittle, K., de Gucht, V, Hurkmans, E., Peeter, A.,...Vliet Vlieland, T. *Targeting motivation and self-regulation to increase physical activity among patients with rheumatoid arthritis: a randomised controlled trial.* Clinical Rheumatology, 2013: 1-8.
5. Janssen, V., de Gucht, V., van Exel, H., Maes, S. *A self-regulation lifestyle program for post-cardiac rehabilitation patients has long-term effects on exercise adherence.* Journal of Behavioral Medicine, 2014. 37(2): 308-21.
6. Sniehotta, F., Scholz, U., Schwarzer, R., Fuhrmann, B., Kiwus, U, Völler, H. *Long-term effects of two psychological interventions on physical exercise and self-regulation following coronary rehabilitation.* International Journal of Behavioral Medicine, 2005. 12(4): 244-255.
7. Christensen, A.J, Moran, P.J., Wiebe-JS, Ehlers, S.L., Lawton, W.J. *Effect of a behavioral self-regulation intervention on patient adherence in hemodialysis.* Health Psychology, 2002. 21(4): 393-397.
8. Marques, M., De Gucht, V., Gouveia, M.J., Cordeiro, A., Maes, S., *Psychometric properties of the Portuguese version of the Checklist of Individual Strength (CIS20-P).* Psychology, Community & Health, 2013. 22(1): 11-18.
9. Vercoulen, J., Alberets, M., Bleijenberg, G. *De Checklist Individual Strenght (CIS).* Gedragstherapie, 1999. 32: 31-36.
10. Vercoulen, J.H., Swanink, C.M., Fennis, J.F., Galama J.M., van der Meer, J.W., Bleijenberg, G. *.Dimensional assessment of chronic fatigue syndrome.* Journal of Psychosomatic Research, 1994. 38(5): 383-92.
11. Vercoulen, J.H., Swanink, C.M., Fennis, J.F., Galama J.M:, van der Meer, J.W., Bleijenberg, G. *Prognosis in chronic fatigue syndrome: A prospective study on the natural course.* Journal of Neurology, Neurosurgery, and Psychiatry, 1996. 60: 489-94.
12. Prins, J.B., Bleijenberg, G., Bazelmans, E., Elving, L.D., de Boo, T.M., Severens, J. L.,...,. van der Meer, J.W.M. *Cognitive behaviour therapy for*

chronic fatigue syndrome: a multicentre randomised controlled trial. The Lancet, 2001. 357(9259): 841-847.
13.Beurskens, A., Bültmann, U., Kant, I., Vercoulen, J., Bleijenberg, G., Swaen, G. *Fatigue among working people: validity of a questionnaire measure.* Occupational and Environmental Medicine, 2000. 57(5): 353-357.
14.Aratake, Y., Tanaka, K., Wada, K., Watanabe, M., Aizawa, Y. *Development of Japanese version of the checklist individual strength questionnaire in a working population.* Journal of Occupational Health, 2007. 49(6): 453-60.
15.Ware JE, Kosinski M, Turner-Bowker DM, Gandek B: *How to score version 2 of the SF-12® Health Survey*. Lincoln, RI: Quality Metric Incorporated; 2002.
16.Leventhal, H., Leventhal, E.A., Contrada, R.J. *Self-regulation, health, and behavior: A perceptual-cognitive approach.* Psychology & Health, 1998. 13(4):717-733.
17.Moss-Morris, R., *Symptom perceptions, illness beliefs and coping in chronic fatigue syndrome.* Journal of Mental Health, 2005. 14: 223-35.
18.Spence, M., Moss-Morris, R., Chalder, T. *The behaviour responses to illness questionnaire (BRIQ): a new predictive measure of medically unexplained symptoms following acute infection.* Psychological Medicine. 2005. 35: 583-593.
19.National Institute for Health and Clinical Excellence (NICE). Clinical guidelines53. Chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy: diagnosis and management of CFS/ME in adults and children. London: 2007.
20.Malouff, J. M., Thorsteinsson, E. B., Rooke, S. E., Bhullar, N., Schutte, N. S. *Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: A meta-analysis.* Clinical Psychology Review, 2008. 28(5): 736-745.
21.Castell B.D., Kazantsis, N., Moss-Morris, R. *Cognitive Behavioral Therapy and Graded Exercise for Chronic Fatigue Syndrome: A Meta-Analysis.* Clinical Psychology Science and Practice, 2011. 18(4): 311-324.
22.Miller WR, Rollnick S. *Motivational interviewing: Helping people change*. 3rd edition ed. 2012, NY: The Guiford Press.
23.Nijs, J., Paul, L., Wallman, K. *Chronic fatigue syndrome: an approach combining self-management with graded exercise to avoid exacerbations.* Journal of Rehabilitation Medicine, 2008. 40: 241-247.
24. Price J.R., Mitchell E., Tidy E., Hunot, V. *Cognitive behaviour therapy*

for chronic fatigue syndrome in adults. Cochrane Database Syst Rev, 2008. 3: CD001027.
25. Edmonds, L., McGuire, L., Price, J. *Exercise Therapy for Chronic Fatigue Syndrome.* Cochrane Database Syst Rev, 2004. 3: CD003200.
26. Tudor-Locke, C., Craig, C., Aoyagi, Y., Bell, R.,..., Blair, S. *How many steps/day are enough? For older adults and special populations.* International Journal of Behavioral Nutrition and Physical Activity, 2011. 8(1): 80.
27. Carver, C.S. Scheier, M.F. *On the self-regulation of behavior*. 1998, New York: University Press.
28. Heijmans, M.J., *Coping and adaptive outcome in chronic fatigue syndrome: importance of illness cognitions.* Journal of Psychosomatic Research, 1998. 45(1): 39-51.
29. Deci, E., Ryan, R. *The 'what' and 'why' of goal pursuits: Human needs and the self-determination of behavior.* Psychological Inquiry, 2000. 11: 227-268.
30. Sheldon, K.M., Elliot, A.J. *Goal striving, need satisfaction, and longitudinal well-being: the self-concordance model.* Journal of Personality and Social Psychology, 1999. 76(3):482-97.
31. Koestner, R., Otis, N., Powers, T.A., Pelletier, L., Gagnon, H. *Autonomous motivation, controlled motivation, and goal progress.* Journal of Personality, 2008. 76(5): 1201-30.
32. Teixeira, P.J., Carraça, E.V., Markland, D., Silva, M.N., Ryan, R. *Exercise, physical activity, and self-determination theory: A systematic review.* International Journal of Behavioral Nutrition and Physical Activity, 2012. 9(1): 78.
33. Deary, V., *A precarious balance: using a self-regulation model to conceptualize and treat chronic fatigue syndrome.* British Journal of Health Psychology, 2008. 13: p. 231-236.
34. Michie, S., Abraham, C., Whittington, C., McAteer, J., Gupta, S. *Effective techniques in healthy eating and physical activity interventions: A meta-regression.* Health Psychology, 2009. 28(6): 690-701.
35. Bélanger-Gravel, A., Godin, G., Amireault, S. *A meta-analytic review of the effect of implementation intentions on physical activity.* Health Psychology Review, 2011. 7(1): p. 23-54.
36. Gollwitzer, P.M. Sheeran, P. *Implementation Intentions and Goal Achievement: A Meta analysis of Effects and Processes*, in *Advances in Experimental Social Psychology*, P.Z. Mark, Editor. 2006, Academic Press.

p. 69-119.
37. Kwasnicka, D., Presseau, J., White, M., Sniehotta, F.F. *Does planning how to cope with anticipated barriers facilitate health-related behaviour change? A systematic review.* Health Psychology Review, 2013. 7(2): 129-145.
38. Sniehotta, F.F., U. Scholz, and R. Schwarzer, *Bridging the intention–behaviour gap: Planning, self-efficacy, and action control in the adoption and maintenance of physical exercise.* Psychology & Health, 2005. 20(2): p. 143-160.
39. Knittle, K., Maes, S., de Gucht, V. *Psychological interventions for rheumatoid arthritis: Examining the role of self-regulation with a systematic review and meta-analysis of randomized controlled trials.* Arthritis Care & Research, 2010. 62(10):1460-1472.
40. Janssen V., de Gucht, V., Dusseldorp, E., Maes, S. *Lifestyle modification programmes for patients with coronary heart disease : a systematic review and meta-analysis of randomized controlled trials.* European Journal of Preventive Cardiology, 2012. 20(4):620-640.
41. National Institute for Health and Clinical Excellence: *Guideline 53: chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy)*. London, 2007.
42. Wiborg, J.F., Knoop, H., Stulemeijer, M., Prins, J.B:, Bleijenberg, G *How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity.* Psycholoical Medicine, 2010. 40(8): 1281-7.
43. Heins, M.J., Knoop, H., Burk, W.J., Bleijenberg, G., *The process of cognitive behaviour therapy for chronic fatigue syndrome: which changes in perpetuating cognitions and behaviour are related to a reduction in fatigue?* Journal of Psychosomatic Research, 2013. 75(3): 235-41.
44. Knoop, H., Prins, J.B., Moss-Morris, R., Bleijenberg, G. *The central role of cognitive processes in the perpetuation of chronic fatigue syndrome.* Journal of Psychosomatic Research, 2010. 68(5): 489-94.
45. Van Houdenhove, B., Luyten, P. *Customizing treatment of chronic fatigue syndrome and fibromyalgia: the role of perpetuating factors.* Psychosomatics, 2008. 49(6): 470-7.
46. Rothman, A.J., *Toward a theory-based analysis of behavioral maintenance.* Health Psychology, 2000. 19(1, Suppl): p. 64-69.
47. Morton, K., Beauchamp, M., Prothero, A., Joyce, L.,...,Pedlar, C. *The effectiveness of motivational interviewing for health behaviour change in*

primary care settings: a systematic review. Health Psychology Review, 2014: 1-19.
48. Ordem dos Psicólogos Portugueses, *Evidência Cientifica sobre custo-efetividade de intervenções psicológicas em cuidados de saúde*. 2011.
49. White, P.D., Goldsmith, K.A., Johnson, A.L., Potts, L.,..., Sharpe, M. *Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial.* The Lancet, 2011. 377(9768): 823-836.
50. Tummers, M., Knoop, H., van Dam, A., Bleijenberg, G. *Moderators of the treatment response to guided self-instruction for chronic fatigue syndrome.* Journal of Psychosomatic Research, 2013. 74(5): 373-377.
51. Dechartres, A., Boutron, I., Tringuart, L., Charles, P., Ravaud, P. *Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study.* Annals of Internal Medicine, 2011. 155(1):39-51.
52. Unverzagt, S., Prondzinsky, R., Peinemann, F. *Single-center trials tend to provide larger treatment effects than multicenter trials: a systematic review.* Journal of Clinical Epidemiology, 2013. 66(11): 1271-1280.
53. Burgess, M., Andiappan, M., Chalder, T. *Cognitive Behaviour Therapy for Chronic Fatigue Syndrome in Adults: Face to Face versus Telephone Treatment - A Randomized Controlled Trial.* Behavioural and Cognitive Psychotherapy, 2012. 40(02): 175-191
54. Friedberg, F., Napoli, A., Coronel, J., Adamowicz, J.,...,Meng, H. *Chronic fatigue self-management in primary care: a randomized trial.* Psychosomatic Medicine, 2013. 75(7): 650-7.
55. Moyers, T.B., Martin, T., Manuel, J.K., Hendrinckson, .S.M, Miller, W.R. *Assessing competence in the use of motivational interviewing.* Journal of Substance Abuse and Treatment, 2005. 28(1): 19-26.
56. Ranjith, G., *Epidemiology of chronic fatigue syndrome.* Occupational Medicine, 2005. 55(1): 13-19.
57. Degoratis, L., Brief Symptom Inventory: Administration, Scoring and Procedures Manual, 1993.
58. Canavarro, M.C., *Inventario de sintomas psicopatologicos BSI.* Testes e provas psicologicas em Portugal Volume 2, 1999: p. 87-109.
59. Lehman, A.M., Lehman, D.R., Hemphill, K.J., Mandel, D.R., Cooper, L.M. *Illness experience, depression, and anxiety in chronic fatigue syndrome.* Journal of Psychosomatic Research, 2002. 52(6): 461-465.

60. Powell, P., Bentall, R.P., Nye, F.J, Edwards, R.H. *Patient education to encourage graded exercise in chronic fatigue syndrome: 2-year follow-up of randomised controlled trial.* The British Journal of Psychiatry, 2004. 184(2): 142-146.
61. Nijs, J., Roussel, N., Van Oosterwijck, J., de Kooning, M.,..., Lundberg, M. *Fear of movement and avoidance behaviour toward physical activity in chronic-fatigue syndrome and fibromyalgia: state of the art and implications for clinical practice.* Clinical Rheumatology, 2013. 32(8): 1121-1129.
62. Wearden, A.J., Dunn, G., Dowrick, C., Morris, R.K. *Depressive symptoms and pragmatic rehabilitation for chronic fatigue syndrome.* British Journal of Psychiatry, 2012. 201(3): 227-32.
63. Sniehotta, F.F., Presseau, J., Hobbs, N., Araújo-Soares, V. *Testing self-regulation interventions to increase walking using factorial randomized N-of-1 trials.* Health Psychology, 2012. 31(6): 733-7.
64. Huibers, M.J., Beurskens, A.J., Van Shayck, C.P., Bazelmans, E.,..., Bleijenberg, G. *Efficacy of cognitive behavioral therapy by general practitioners for unexplained fatigue among employees: randomized controlled trial.* British Journal of Psychiatry, 2004. 184: 240-246.

Nederlandse Samenvatting

De focus van dit proefschrift ligt op de rol van zelfregulatie en lichaamsbeweging bij het omgaan met chronische vermoeidheid. Wij hebben een op zelfregulatie gebaseerde interventie die zich richt op lichaamsbeweging (LB) bij patiënten met (het) chronische vermoeidheid(ssyndroom) (CV(S)) ontwikkeld, geïmplementeerd en geëvalueerd. Deze interventie is genaamd 'de 4 STAPPEN naar controle over je vermoeidheid'[1]. Bij de evaluatie zijn we ook nagegaan of veranderingen in de intermediaire doelen van de interventie (zelfregulatie vaardigheden en lichaamsbeweging) de veranderingen in de ernst van de vermoeidheid verklaarden.

Voorafgaand aan deze interventie studie hebben we een serie onderzoeken uitgevoerd die van belang waren voor de ontwikkeling van de interventie en de evaluatie van de effecten middels een gecontroleerde studie (Randomized Controlled Trial (RCT)): (1) de validatie van een meetinstrument voor het bepalen van de ernst van de vermoeidheid (primair einddoel) in de taal en voor de doelgroep waar we de interventie wilden implementeren (Portugal), (2) een vergelijking van klinische kenmerken en gedragsmatige en cognitieve determinanten van CV(S) in een Nederlandse en Portugese patiëntengroep, en (3) een systematische review en meta-analyse van de gedragsmatige en psychologische interventies met een component gericht op het gradueel opvoeren van lichaamsbeweging uitgevoerd bij CV(S) patiënten.

De meting van vermoeidheid

De eerste empirische studie (**Hoofdstuk 2**) beschrijft de psychometrische kenmerken van de Portugese versie van de Checklist Individuele Spankracht (Checklist of Individual Strength (CIS20-P; [2]). De CIS20 [3], een multidimensionaal zelf-rapportage instrument dat zowel de fysieke als de mentale vermoeidheid omvat, is een gevalideerde maat ontwikkeld voor CVS patiënten en is breed gebruikt binnen deze (bijv. [4]) en andere populaties (bijv. beroepspopulatie; [5]). Voor deze studie zijn gegevens verzameld van een grote steekproef gezonde volwassenen (N= 430) en van een steekproef CV(S) patiënten (N=89).

Onze resultaten lieten een goede convergente validiteit van de CIS20-P zien met een maat voor Vitaliteit en een maat voor Fysiek en Psychologisch Functioneren, bepaald met de SF-12v2 [6]. De CIS20-P kon ook adequaat onderscheid maken tussen gematchte gezonde en CV(S) onderzoeksgroepen. Patienten met CV(S) lieten significant hogere niveau's van vermoeidheid zien op alle subschalen en op de totale vermoeidheidsscore (Total CIS20-P). Interne consistentie indicatoren van alle subschalen en de totale vermoeidsheidsscore waren voldoende, met uitzondering van de schaal Motivatie. Daarnaast ondersteunden de resultaten de multidimensionale (vier-factor) structuur van de CIS20-P, maar enkele van de adjustment indices of fit van het model waren onvoldoende, met name in de CV(S) groep. Het geringe aantal participanten in de CV(S) groep kan een rol hebben gespeeld bij de meer matige indicatoren in deze groep.

Van Determinanten ...

Hoofdstuk 3 richt zich op een cross-culturele vergelijking van klinische karakteristieken en gedragsmatige en psychologische determinanten van CVS tussen een Portugese en een Nederlandse CV(S) patiëntengroep. We hebben een gelijksoortig vragenlijstonderzoek uitgevoerd met vergelijkbare onderzoeksgroepen (vrouwelijke patiënten met CVS) in Nederland (N=167) en Portugal (N=85). Het doel van de studie was om de ernst van de vermoeidheid, somatische klachten, psychologische klachten (depressie en angst) en gezondheidsgerelateerde Kwaliteit van Leven (Health-related Quality of Life (HrQoL)) in Portugese en Nederlandse CVS patiënten te vergelijken, en de differentiële effecten van zelfregulatie cognities (ziekte cognities) en gedrag (lichaamsbeweging en ongunstige gedragsregulatie patronen – zich (overmatig) beperkend gedrag en 'alles of niets' gedrag) op ernst van de vermoeidheid te exploreren.

In lijn met de verwachtingen, was de ernst van de vermoeidheid vergelijkbaar in de twee onderzoeksgroepen. Het hoge niveau van somatische klachten, de ongunstige fysieke en mentale Kwaliteit van Leven, en het hoge percentage patiënten dat niet werkzaam was in beide groepen, reflecteren de beperkingen die algemeen gevonden worden in CVS patiënten [7]. Verder vonden we dat hoge

niveaus van vermoeidheid en bijkomende somatische klachten waren gerelateerd aan een lage Kwaliteit van Leven. Daarnaast liet de Portugese onderzoeksgroep de meest ongunstige scores zien op psychologisch functioneren, en had hogere depressie en angst scores.

Ziekte cognities en gedragsmatige factoren waren in beide onderzoeksgroepen significant geassocieerd met ernst van vermoeidheid. Met betrekking tot ziekte cognities, waren onze resultaten in lijn met eerder onderzoek dat liet zien dat positieve ziekte cognities gepaard gaan met lagere ernst van de vermoeidheid, en negatieve ziekte cognities gepaard gaan met sterkere ernst van de vermoeidheid. [8]. Echter, er waren verschillen in de specifieke cognities. Bij de Portugese patiënten zagen we dat het toeschrijven van meer symptomen aan de ziekte en het rapporteren van een sterkere emotionele impact van het hebben van CVS gerelateerd was aan sterkere vermoeidheid. Wat betreft de gedragsmatige determinanten in de Portugese patiëntengroep bleek dat hogere niveaus van lichaamsbeweging positief samenhingen met verbetering in vermoeidheid, en dat zich beperkend gedrag daarentegen verband hield met ernstigere vermoeidheid. In de Nederlandse patiëntengroep, die meer aan lichaamsbeweging deed, bleek het hanteren van een alles-of-niets gedragsregulatie patroon significant samen te hangen met een hogere ernst van de vermoeidheid. Deze onderzoeksresultaten laten overeenkomsten en verschillen zien in de klinische kenmerken en cognitieve en gedragsdeterminanten van CVS die van belang zijn voor de behandelingsmogelijkheden.

...naar Interventies

Vervolgens, wordt in **Hoofdstuk 4** een systematische review en meta-analyse gepresenteerd over de effectiviteit van gedragsmatige en psychologische behandelingen voor patiënten met CV(S) die focussen op een geleidelijke opbouw van lichaamsbeweging. Het eerste doel van deze meta-analyse was om het algehele effect van interventies op zowel lichaamsbeweging als op ernst van de vermoeidheid, fysiek functioneren en psychologische klachten van CV(S) patiënten vast te stellen. Uitsluitend gecontroleerde (RCT) studies werden hierbij meegenomen, waarbij een of meerdere

interventie condities werden vergeleken met (een) controle conditie(s).

In totaliteit laten de resultaten zien dat interventies (k=16) een gunstig medium effect hadden op verbetering van vermoeidheid, en kleine effecten hadden op fysiek functioneren, lichaamsbeweging, en psychologische klachten, bij de nameting na interventie, en bij lange-termijn follow-up (tot 17 maanden). Een uitzondering was zichtbaar voor lichaamsbeweging bij de nameting – hierbij was uitsluitend een tendens in de gunstige richting zichtbaar.

Aangezien de interventie effecten sterk verschilden tussen de verschillende studies, werden in deze meta-analyse ook mogelijke moderatoren van het interventie effect onderzocht. Deze potentiele moderatoren betroffen het type zorg dat aangeboden werd in de controle conditie, de behandelsetting, de duur van de interventie, de behandelaar / uitvoerder van de interventie, de aanwezigheid van een psychologische (cognitieve) component (versus uitsluitend gedragsgerichte interventies), minimale vormen van direct behandelaar-patiënt contact (versus meer intensieve interventies), en een flexibele aanpak van lichaamsbeweging (aanpassing van lichaamsbewegingsniveaus of doelen aan individuele grenzen). Hoewel de conclusies die van deze subgroep analyses getrokken kunnen worden enigszins beperkt worden door het geringe aantal studies, laten de resultaten zien dat een aantal van de genoemde variabelen moderatoren waren van het interventie effect. Dit was echter uitsluitend het geval voor de effecten op vermoeidheid en depressieve klachten. Interventies die aangeboden werden door psychologen of psychotherapeuten en interventies die in secundaire of tertiaire zorg instellingen uitgevoerd werden lieten sterkere gunstige effecten zien. Daarnaast, interventies met minimaal direct contact met patiënten lieten gunstige effecten zien op ernst van de vermoeidheid en depressieve klachten. Verder vonden we dat interventies die flexibiliteit toestonden in het niveau van lichaamsbeweging en het te stellen doel sterkere effecten hadden op depressieve klachten. We vonden geen significante verschillen in de effecten van interventies die zich uitsluitend richtten op lichaamsbeweging of degenen die zich ook richtten op psychologische factoren, hoewel de resultaten in de richting lijken te wijzen van een groter effect van de laatste groep interventies daar waar het gaat om vermoeidheid en depressieve klachten.

Deze resultaten leveren waardevolle aanknopingspunten voor de focus en vorm van toekomstige interventies voor het omgaan met chronische vermoeidheid.

Gebaseerd op de eerdere studies, geeft **Hoofdstuk 5** het protocol van de '4 STAPPEN naar controle over je vermoeidheid' trial. In het onderzoeksprotocol presenteren we de theoretische en empirische onderbouwing voor de ontwikkeling en implementatie van de 4 STAPPEN bij CV(S) patiënten, de doelen van de RCT, en een gedetailleerde beschrijving van de methoden en procedures.

De '4 STAPPEN' trial werd onderzocht in diverse eerstelijns gezondheidscentra en in de Portugese Patiënten Associatie. Patiënten die bereid waren te participeren in de RCT werden random toegewezen aan de controle conditie (standaard zorg + een brochure met informatie over lichaamsbeweging) of de interventie conditie (standaard zorg + 4 STAPPEN programma). Patiënten in deze experimentele conditie kregen een kortdurende interventie (12 weken) met minimaal direct contact (maximaal 3 uur totale contact tijd). De 4 stappen bestond uit een combinatie van Motiverende Gespreksvoering (Motivational Interviewing) [9], met training in zelfregulatie vaardigheden [1]. Deelnemers stelden en planden een relevant lichaamsbewegingsdoel, en werden geadviseerd om geleidelijk hun lichaamsbeweging op te bouwen op basis van een persoonlijk flexibel schema [10]. Patiënten ontvingen handleidingen met informatie over CV(S) en (gebrek aan) lichaamsbeweging en ontvingen op zelfregulatie gebaseerde handleidingen die ingingen op zelfregulatie cognities en vaardigheden voor iedere fase van het proces op weg naar het doel. Om patiënten te ondersteunen bij dit proces, ontvingen zij in aanvulling hierop telefonische op zelfregulatie gebaseerde begeleiding, als ook een stappenteller en een dagelijkse activiteiten dagboek, dat gebruikt kon worden om de dagelijkse bewegingsactiviteit te monitoren tijdens de interventie periode.

Metingen werden uitgevoerd bij de nulmeting, na de interventie (3 maanden), en bij de follow-up (12 maanden). De primaire uitkomstmaat was de subjectief ervaren

vermoeidheid (CIS20-P Subjective Experience of Fatigue subschaal). Secondaire uitkomstmaten die werden onderzocht in de diverse hoofdstukken van dit proefschrift betroffen Ernst van de vermoeidheid (Totaalscore CIS20-P), Impact van de vermoeidheid, gezondheidsgerelateerde Kwaliteit van leven, somatische klachten en psychologische klachten (depressie en angst). Om zicht te krijgen op de verschillende vormen van lichaamsbeweging die de CV(S) patiënten ondernamen, bepaalden we (1) aantal stappen per dag (stappenteller), (2) Lichaamsbeweging in de vrije tijd (Matig tot intensieve lichaamsbeweging), en (3) progressie t.a.v. c.q. het bereiken van het lichaamsbewegingsdoel. Daarnaast hebben we na afloop van de interventie gemeten in hoeverre zelfregulatie vaardigheden toegepast werden om persoonlijke doelen te bereiken

De nametingresultaten van de 4 STAPPEN trial zijn besproken in de empirische studie weergegeven in **Hoofdstuk 6** en de lange-termijn resultaten zijn terug te vinden in **Hoofdstuk 7**.

Gegevens van 84 patiënten die random toegewezen waren aan de condities en de nulmeting hadden ingevuld werden meegenomen in de analyse. De meeste patiënten waren van middelbare leeftijd (~48 jaar), van het vrouwelijke geslacht (97.8%), en ongeveer de helft van de onderzoeksgroep had geen betaald werk. Slechts twee deelnemers stopten tijdens de interventie-periode, en de gehele uitval was 25% bij de nameting en 33% bij de follow-up.

Bij de nameting verschilden de interventie en de controle groep significant, met een medium effect, op Ernst van de vermoeidheid. Een mixed design analyse, waarbij werd gecontroleerd voor duur van de ziekte en setting, liet eveneens een significant tijd x groep effect zien in de verbetering in ernst van de vermoeidheid. Daarnaast lieten de patiënten die het 4 STAPPEN programma hadden ontvangen een significante verbetering in fysiek en psychologisch Kwaliteit van Leven zien. Daarentegen vonden we geen significant effect van het 4 STAPPEN programma in het reduceren van psychologische klachten of somatische klachten. Lichaamsbeweging was een van de hoofddoelen van het 4 STAPPEN programma. Bij de nameting vonden we alleen een tendens in de richting van een gemiddeld hoger aantal stappen per dag in de interventie groep. Met betrekking tot lichaamsbeweging

in de vrijetijd was een duidelijke toename tussen nulmeting en nameting zichtbaar in de interventie groep. Daarnaast was in de interventie groep een significant hoger percentage deelnemers fysiek actief. Tenslotte bleek het 4 STAPPEN programma een sterk effect te hebben op de progressie van patiënten richting hun persoonlijke lichaamsbewegingsdoel.

Bij de follow-up (Hoofdstuk 7), werd een groter verschil in de subjectief ervaren Ernst van de vermoeidheid tussen de interventie en de controle conditie gevonden, en was er sprake van een aanzienlijke toename, met circa 21%, in het percentage patiënten die niet-klinische niveaus van vermoeidheid lieten zien in de interventiegroep ten opzichte van het ontbreken van dergelijke subklinische niveaus in de controle groep patiënten. Tussen de nameting en de follow-up werden de gunstige effecten van het 4 STAPPEN programma gehandhaafd met sterkere effecten ten opzichte van de nulmeting, en er was daarnaast een significant effect zichtbaar op de impact van vermoeidheid in het dagelijkse leven. In dezelfde lijn vonden we zich doorzettende gunstige effecten op fysiek functioneren en sterkere effecten op psychologische Kwaliteit van Leven. Significante interventie effecten op somatische klachten en psychologische klachten bleven uit. Met betrekking tot lichaamsbeweging werden de verschillen tussen de groepen in dagelijkse aantal stappen gering. Desalniettemin, het gemiddeld aantal stappen per dag voldeed aan de minimale richtlijnen voor patiënten met een chronische ziekte [11]. Ten aanzien van lichaamsbeweging in de vrije tijd was geen significant tijd x groep effect zichtbaar tussen nameting en follow-up. In lijn met hetgeen dat bij de nameting zichtbaar was, was er in de interventie groep sprake van een significant hoger percentage lichamelijk actieve deelnemers (66%; vs. 36% in de controle groep).

Het laatste doel van dit proefschrift, dat aan de orde komt in **Hoofdstuk 7**, was het onderzoek naar het mechanisme via welke de interventie de blijvende effecten liet zien op de primaire uitkomst van het 4 STAPPEN programma: de subjectieve ervaring van vermoeidheid. Met oog op dit doel hebben we mediatie-analyses uitgevoerd waarbij werd nagegaan in hoeverre de op basis van empirie en theorie gestelde intermediaire doelen –

lichaamsbeweging en zelfregulatie vaardigheden – bijdroegen aan de vermindering van vermoeidheid.

Met betrekking tot lichaamsbeweging, hebben we een mediatie analyse uitgevoerd met dagelijkse aantal stappen vastgesteld met de stappenteller (een vrij objectieve maat voor lichaamsbeweging) en ervaren progressie t.a.v. het lichaamsbewegingsdoel. De resultaten lieten zien dat verbetering in vermoeidheid bij de follow-up deels verklaard kan worden door de progressie en het bereiken van het persoonlijke lichaamsbewegingsdoel bij de nameting. Wat betreft het gebruik van zelfregulatie vaardigheden in het streven naar een persoonlijk gedragsveranderingsdoel, gaven de deelnemers in de interventie conditie bij de nameting aan vaker gebruik te maken van zelfregulatie vaardigheden (bijv. actie plannen maken) in vergelijking met deelnemers in de controle conditie. Mediatie analyse liet zien dat het vaker gebruik maken van zelfregulatie strategieën om persoonlijke gedragsveranderingsdoelen te bereiken (bij de nameting) bijdroeg aan een verbetering in vermoeidheid bij de follow-up.

De resultaten van de 4 STAPPEN trial laten zien dat een kortdurende op zelfregulatie gebaseerde interventie een gunstig en blijvend effect kan hebben in het omgaan met chronische vermoeidheid en dat progressie in de richting van en het bereiken van persoonlijke lichaamsbewegingsdoelen en een toename in het gebruik van zelfregulatie vaardigheden deels verantwoordelijk zijn voor deze blijvende verbetering in vermoeidheid.

Referenties

1. Maes, S., Karoly, P. *Self-regulation assessment and intervention in physical health and illness: a Review.* Applied Psychology: International Review, 2005. 54(29): 267-299.
2. Marques, M., De Gucht, V., Gouveia, M.J., Cordeiro, A., Maes, S., *Psychometric properties of the Portuguese version of the Checklist of Individual Strength (CIS20-P).* Psychology, Community & Health, 2013. 22(1): 11-18.
3. Vercoulen, J., Alberets, M., Bleijenberg, G. *De Checklist Individual Strenght (CIS).* Gedragstherapie, 1999. 32: 31-36.
4. Vercoulen, J.H., Swanink, C.M., Fennis, J.F., Galama J.M:, van der Meer, J.W., Bleijenberg, G. *Prognosis in chronic fatigue syndrome: A prospective study on the natural course.* Journal of Neurology, Neurosurgery, and Psychiatry, 1996. 60: 489-94.
5. Beurskens, A., Bültmann, U., Kant, I., Vercoulen, J., Bleijenberg, G., Swaen, G. *Fatigue among working people: validity of a questionnaire measure.* Occupational and Environmental Medicine, 2000. 57(5): 353-357.
6. Ware JE, Kosinski M, Turner-Bowker DM, Gandek B: *How to score version 2 of the SF-12® Health Survey*. Lincoln, RI: Quality Metric Incorporated; 2002.
7. Afari, N., Buchwald, D. *Chronic Fatigue Syndrome: A Review.* American Journal of Psychiatry, 2003. 160: 221-236.
8. Moss-Morris, R., *Symptom perceptions, illness beliefs and coping in chronic fatigue syndrome.* Journal of Mental Health, 2005. 14: 223-35.
9. Miller WR, Rollnick S. *Motivational interviewing: Helping people change*. 3rd edition ed. 2012, NY: The Guiford Press.
10. Nijs, J., Paul, L., Wallman, K. *Chronic fatigue syndrome: an approach combining self-management with graded exercise to avoid exacerbations.* J Rehabil Med, 2008. 40: 241-247.
11. Tudor-Locke, C., Craig, C., Aoyagi, Y., Bell, R.,..., Blair, S. *How many steps/day are enough? For older adults and special populations.* Int J Behav Nutr Phys Act, 2011. 8(1): 80.

Curriculum Vitae

Marta Marques was born on November 21, 1981 in Porto, Portugal. She completed her secondary education at Escola Secundária de Cascais in 1999. In 2005, she graduated (licenciate) in Applied Psychology (specialization in Clinical Psychology) at ISPA-University Institute, Portugal. After graduating she worked as a personal counsellor and developed a curriculum of Personal Social and Health Education in the Portuguese American School, collaborated as a research assistant at the Department of Exercise and Health Psychology and became assistant in ISPA, teaching several courses at the BSc and MSc levels. She did a postgraduation course in Psychology of Sport and Physical activity at ISPA (2006) and pursued a Research Master's degree in Health Psychology in the same institution, graduating with honours in 2008. She started her PhD project in 2009 at Leiden University with a 4-years research grant from the Portuguese Science Foundation. During this period she did advanced training in Cognitive-Behavioural Therapy and Motivational Interviewing. She was recently appointed as a research associate in the Faculty of Human Kinetics, University of Lisbon, and continues to teach at ISPA.

Acknowledgements

First and foremost, I am heartily thankful to my PhD promotor Stan Maes, my mentor for the past years. From day one, you believed in my capabilities as a researcher, promptly accepting to supervise my Master thesis, and later accepting me as a PhD student in Leiden. Your knowledge and passion for Health Psychology is truly inspirational! You have always provided me with the support to become an independent researcher and for that I will always be grateful. Your encouragement and priceless advices have been instrumental in my growth as a researcher and a person. I truly feel honoured to have you as my promotor. I also want to express my gratitude to my co-promotor, Verónique de Gucht. Thank you for your invaluable guidance (and for always answering my questions promptly), and for you patient and encouragement throughout my PhD, which was crucial for the completion of this thesis. Your expertise and scientific rigour definitely improved the quality of this work. It was a pleasure to have you as my co-promotor.

I am grateful to Maria João Gouveia, my first mentor and "Camarada de Luta", were it not for you, I probably wouldn't be a researcher. Thank you for being a constant source of encouragement and support, and for your invaluable advices through the years. You are an incredible colleague and friend.

To João, my partner, thank you for believing in me, for being so proud of my achievements, and for staying by my side when I was working 24/7. You are the kindest person I ever met and I am lucky to have you in my life. To my family, thank you all for being present in my life in such proximity and love. A special word to my sister for always holding my hand, and remind me that anything is possible. To my parents, thank you for the stimulating environment in which I grew up, and for always respecting my pursuits throughout my life. To my brother and niece, thank you for reminding me that there is more to life than work. A special thanks to my cousin Mariana for designing such an awesome cover and layout for my thesis. I am

indebted to all my friends who have supported me over the last few years.

To my colleagues from the Health Psychology Unit and from the "Comité Central" in ISPA, thank you for your friendship. Isabel Leal, thank you for providing the resources to conduct this research in ISPA. I would like to thank Teresa for her encouragement and support while I was in the Netherlands, specially at the beginning of this journey. I would like to thank Keegan and Veronica from Leiden University for their valuable input based on their own experiences throughout their PhD studies. Margot van der Doef, thank you for your precious help with the translation of the summary to Dutch language. I am also thankful to both Veronica and Margot for being my paranimfen. I would like to thank Pauline Ruygrok for taking care of the logistics that made my visits to Leiden much easier. I would also like to thank Pedro Teixeira for the support to write up this thesis in the last year.

I am grateful to my dissertation committee, for sparing their time to review this thesis.

I would like to thank the medical doctors (especially Tia Odete), and the directors of the centres and MYOS for their active collaboration in this research. And last but not least, I would like to thank all patients who participated in the 4-STEPS trial, thank you for sharing your experiences and for being available, in spite of so many daily challenges.